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**UNITED STATES PATENT APPLICATION**

**FOR**

**METHOD OF MAKING TRICYCLIC AMINOCYANOPYRIDINE  
COMPOUNDS**

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## METHOD OF MAKING TRICYCLIC AMINOCYANOPYRIDINE COMPOUNDS

### CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

5     **[0001]**     This application claims the benefit of U.S. Provisional Patent  
Application Serial No. 60/432,783, filed December 12, 2002, which is  
incorporated by reference herein in its entirety. This application is related  
to commonly assigned and copending applications having the titles  
“Method of using aminocyanopyridine compounds as mitogen activated  
10     protein kinase-activated protein kinase-2 inhibitors” (and having  
Provisional Application Serial No. 60/432,807), and “Tricyclic  
aminocyanopyridine inhibitors of mitogen activated protein kinase-  
activated protein kinase-2” (and having Provisional Application Serial No.  
60/432,844), each of which was filed on the same date as the present  
15     application.

### BACKGROUND OF THE INVENTION

(1)     Field of the Invention:

20     **[0002]**     The present invention relates to aminocyanopyridine  
compounds, and in particular, to tricyclic aminocyanopyridine compounds  
which inhibit mitogen-activated protein kinase-activated protein kinase-2  
(MAPKAP-kinase 2, or MK-2), and compositions containing those  
aminocyanopyridine compounds.

(2)     Description of the Related Art:

25     **[0003]**     Mitogen-activated protein kinases (MAPKs) are members of  
conserved signal transduction pathways that activate transcription factors,  
translation factors and other target molecules in response to a variety of  
extracellular signals. MAPKs are activated by phosphorylation at a dual  
phosphorylation motif with the sequence Thr-X-Tyr by mitogen-activated  
protein kinase kinases (MAPKKs). In higher eukaryotes, the physiological  
30     role of MAPK signaling has been correlated with cellular events such as  
proliferation, oncogenesis, development and differentiation. Accordingly,  
the ability to regulate signal transduction via these pathways could lead to

the development of treatments and preventive therapies for human diseases associated with MAPK signaling, such as inflammatory diseases, autoimmune diseases and cancer.

**[0004]** In mammalian cells, three parallel MAPK pathways have been described. The best characterized pathway leads to the activation of the extracellular-signal-regulated kinase (ERK). Less well understood are the signal transduction pathways leading to the activation of the cJun N-terminal kinase (JNK) and the p38 MAPK. See, *e.g.*, Davis, *Trends Biochem. Sci.* 19:470-473 (1994); Cano, *et al.*, *Trends Biochem. Sci.* 20:117-122(1995).

**[0005]** The p38 MAPK pathway is potentially activated by a wide variety of stresses and cellular insults. These stresses and cellular insults include heat shock, UV irradiation, inflammatory cytokines (such as TNF and IL-1), tunicamycin, chemotherapeutic drugs (*i.e.*, cisplatinum), anisomycin, sorbitol/hyperosmolarity, gamma irradiation, sodium arsenite, and ischaemia. See, Ono, K., *et al*, *Cellular Signalling* 12, 1 - 13 (2000). Activation of the p38 pathway is involved in (1) production of proinflammatory cytokines, such as TNF- $\alpha$ ; (2) induction of enzymes, such as Cox-2; (3) expression of an intracellular enzyme, such as iNOS, which plays an important role in the regulation of oxidation; (4) induction of adherent proteins, such as VCAM-1 and many other inflammatory-related molecules. Furthermore, the p38 pathway functions as a regulator in the proliferation and differentiation of cells of the immune system. See, Ono, K., *et al.*, *Id.* at 7.

**[0006]** The p38 kinase is an upstream kinase of mitogen-activated protein kinase-activated protein kinase-2 (MAPKAP kinase-2 or MK-2). (See, Freshney, N. W., *et al.*, *J. Cell*, 78:1039-1049 (1994)). MK-2 is a protein that appears to be predominantly regulated by p38 in cells. Indeed, MK-2 was the first substrate of p38 $\alpha$  to be identified. For example, *in vitro* phosphorylation of MK-2 by p38 $\alpha$  activates MK-2. The substrates that MK-2 acts upon, in turn, include heat shock protein 27, lymphocyte-specific protein 1 (LAP1), cAMP response element-binding

protein (CREB), ATF1, serum response factor (SRF), and tyrosine hydroxylase. The substrate of MK-2 that has been best characterized is small heat shock protein 27 (hsp27).

**[0007]** The role of the p38 pathway in inflammatory-related diseases has been studied in several animal models. The pyridinyl imidazole compound SB203580 has been shown to be a specific inhibitor of p38 *in vivo*, and also has been shown to inhibit activation of MK-2, (See, Rouse, J., *et al*, *Cell*, 78:1027-1037 (1994); Cuenda, A., *et al*, *Biochem. J.*, 333:11-15 (1998)), as well as a MAP kinase homologue termed reactivating kinase (RK). (See, Cuenda, A., *et al.*, *FEBS Lett.*, 364(2):229 - 233 (1995)). Inhibition of p38 by SB203580 can reduce mortality in a murine model of endotoxin-induced shock and inhibit the development of mouse collagen-induced arthritis and rat adjuvant arthritis. See, *e.g.*, Badger, A. M., *et al.*, *J. Pharmacol Exp. Ther.*, 279:1453 - 1461 (1996). Another p38 inhibitor that has been utilized in an animal model that is believed to be more potent than SB203580 in its inhibitory effect on p38 is SB 220025. A recent animal study has demonstrated that SB 220025 caused a significant dose-dependent decrease in vascular density of granulomas in laboratory rats. (See Jackson, J. R., *et al*, *J. Pharmacol. Exp. Ther.*, 284:687 - 692 (1998)). The results of these animal studies indicated that p38, or the components of the p38 pathway, can be useful therapeutic targets for the prevention or treatment of inflammatory disease.

**[0008]** Due to its integral role in the p38 signaling pathway, MK-2 has been used as a monitor for measuring the level of activation in the pathway. Because of its downstream location in the pathway, relative to p38, MK-2 has been measured as a more convenient, albeit indirect, method of assessing p38 activation. However, so far, research efforts exploring therapeutic strategies associated with the modulation of this pathway have focused mainly on the inhibition of p38 kinase.

**[0009]** Several compounds that inhibit the activity of p38 kinase have been described in U.S. Patent Nos. 6,046,208, 6,251,914, and 6,335,340.

These compounds have been suggested to be useful for the treatment of CSBP/RK/p38 kinase mediated disease. Commercial efforts to apply p38 inhibitors have centered around two p38 inhibitors, the pyridinylimidazole inhibitor SKF 86002, and the 2,4,5 triaryl imidazole inhibitor SB203580.

5 See, Lee, J. C., *et al*, *Immunopharmacology* 47, 185-192 (2000).

Compounds possessing a similar structure have also been investigated as potential p38 inhibitors. Indeed, p38 MSP kinase's role in various disease states has been elucidated through the use of inhibitors.

[00010] Kotlyarov, A. *et al*, in *Nat. Cell Biol.*, 1(2):94 - 97 (1999)

10 introduced a targeted mutation into a mouse MK-2 gene, resulting in MK-2-deficient mice. It was shown that mice lacking MK-2 possessed increased stress resistance and survived LPS-induced endotoxic shock better than MK-2<sup>+</sup> mice. The authors concluded that MK-2 was an essential component in the inflammatory response that regulates  
15 biosynthesis of TNF $\alpha$  at a post-transcriptional level. More recently, Lehner, M.D., *et al*, in *J. Immunol.*, 168(9):4667-4673 (2002), reported that MK-2-deficient mice showed increased susceptibility to *Listeria monocytogenes* infection, and concluded that MK-2 had an essential role in host defense against intracellular bacteria, probably via regulation of  
20 TNF and IFN-gamma production required for activation of antibacterial effector mechanisms.

[00011] The location of MK-2 in the p38 signaling pathway at a point that is downstream of p38 offers the potential that MK-2 could act as a focal point for modulating the pathway without affecting as many  
25 substrates as would the regulation of an enzyme further upstream in the signaling cascade -- such as p38 MAP kinase.

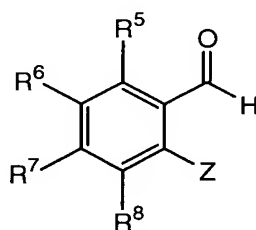
[00012] Accordingly, it would be useful to provide compounds that could serve to modulate the activity of MK-2 -- in particular, to act as inhibitors of MK-2 activity. It would be useful to provide a method of making such  
30 aminocyanopyridine compounds which was simple and straightforward. It would be even more useful if such method could be formulated as a "single pot" method, wherein all reactions that are required for the

production of a tricyclic aminocyanopyridine MK-2 inhibitor can be carried out in a single vessel without removal or transfer of the contents to a separate vessel at some point during the production process.

#### SUMMARY OF THE INVENTION

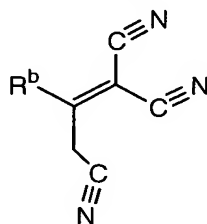
5 [00013] Briefly, therefore the present invention is directed to a novel method of making a tricyclic aminocyanopyridine MK-2 inhibiting compound, the method comprising:

reacting a substituted benzaldehyde having the structure:

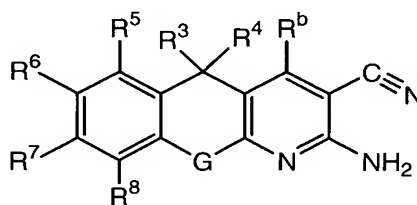


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with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



15

wherein:

Z is selected from the group consisting of -OH, -SH, and -NR<sup>a</sup>Y;

R<sub>a</sub> is selected from the group consisting of alkyl, aryl, and heteroaryl;

Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

5           when G is oxygen, it has no substituent groups;

          when G is sulfur, it is either unsubstituted, or is substituted with one or two oxo groups;

          when G is nitrogen, it is substituted with C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>b</sup> is selected from the group consisting of furyl and -NH-R<sup>2</sup>;

10          R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

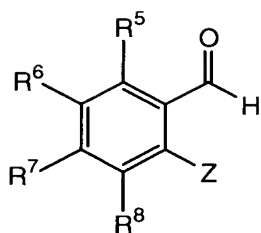
          R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group  
15       consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

          R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group  
20       consisting of hydrogen, hydroxy, alkoxy, halo, alkyl, alkenyl, alkyl, arylalkyl, alkylaryl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylamino, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, alkylcarboxyalkoxy, pyrrolidylethoxy, hydroxyalkoxy, and alkylcarboxy, where R<sup>6</sup> and R<sup>7</sup> are  
25       such that they optionally join to form a six membered heterocyclic ring.

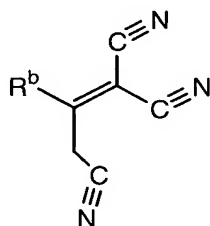
**[00014]** The present invention is also directed to a novel method of making a tricyclic aminocyanopyridine MK-2 inhibiting compound, the method comprising:

          reacting a substituted benzaldehyde having the structure:

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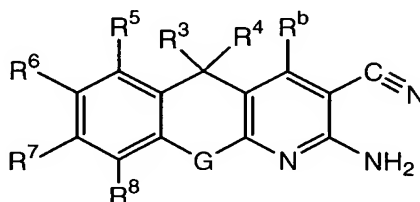


with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:

5



wherein:

Z is selected from the group consisting of -OH, -SH, and -NR<sup>a</sup>Y;

R<sub>a</sub> is selected from the group consisting of alkyl, aryl, and

10

heteroaryl;

Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

15

when G is oxygen, it has no substituent groups;

when G is sulfur, it is either unsubstituted, or is substituted with one or two oxo groups;

when G is nitrogen, it is substituted with C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>b</sup> is selected from the group consisting of furyl and -NH-R<sup>2</sup>;



$R^2$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

5             $R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

10             $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently selected from the group consisting of:

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_1$ - $C_6$  alkoxy, hydroxy  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenoxy,

15            branched or unbranched amino  $C_1$ - $C_6$  alkyl, diamino  $C_2$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino, di-( $C_1$ - $C_6$  alkyl)amino,  $C_1$ - $C_4$  alkoxyarylamino,  $C_1$ - $C_4$  alkoxyalkylamino, amino  $C_1$ - $C_6$  alkoxy, di-( $C_1$ - $C_4$  alkylamino,  $C_2$ - $C_6$  alkoxy, di-( $C_1$ - $C_6$  alkyl)amino  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino  $C_1$ - $C_6$  alkoxy, halo  $C_1$ - $C_6$  alkoxy, dihalo  $C_1$ - $C_6$  alkoxy, trihalo  $C_1$ - $C_6$  alkoxy, cyano  $C_1$ - $C_6$  alkyl, dicyano  $C_1$ - $C_6$  alkyl, cyano  $C_1$ - $C_6$  alkoxy, dicyano  $C_1$ - $C_6$  alkoxy, carbamyl  $C_1$ - $C_4$  alkoxy, heterocyclyl  $C_1$ - $C_4$  alkoxy, heteroaryl  $C_1$ - $C_4$  alkoxy, sulfo, sulfamyl,  $C_1$ - $C_4$  alkylaminosulfonyl, hydroxy  $C_1$ - $C_4$  alkylaminosulfonyl, di-( $C_1$ - $C_4$  alkyl)aminosulfonyl,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkylsulfonyl,  $C_1$ - $C_4$  alkylsulfinyl,

25            aryl, aryl  $C_1$ - $C_6$  alkyl, heterocyclyl  $C_1$ - $C_6$  alkyl, heteroaryl  $C_1$ - $C_6$  alkyl, heterocyclyl  $C_1$ - $C_6$  alkoxy, heteroaryl  $C_1$ - $C_6$  alkoxy, aryl  $C_1$ - $C_6$  alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted, the substituent group is selected from one or more of the group consisting of  $C_1$ - $C_6$  alkyl, halo, amino, and  $C_1$ - $C_6$  alkoxy,

30            substituted or unsubstituted  $C_3$ - $C_6$  cyclyl,  $C_3$ - $C_6$  heterocyclyl, and, if substituted, the substituent group is selected from one or more of the

group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, amino, and where the C<sub>3</sub>-C<sub>6</sub> heterocyclyl ring contains O, S, or N,

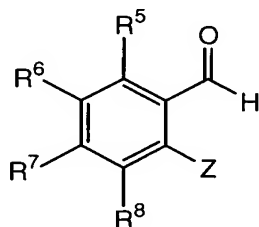
5 branched or unbranched C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkoxy, and  
carboxy, carboxy C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub>  
alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl.

[00015] Among the several advantages found to be achieved by the  
present invention, therefore, may be noted the provision of a method of  
making a tricyclic aminocyanopyridine MK-2 inhibiting compound which  
was simple and straightforward; and also the provision of such a method  
10 that is a "single pot" method, wherein all reactions that are required for the  
production of a tricyclic aminocyanopyridine MK-2 inhibitor can be carried  
out in a single vessel without removal or transfer of the contents to a  
separate vessel at some point during the production process.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

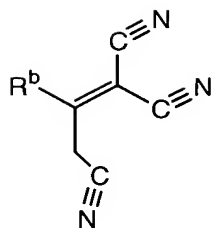
15 [00016] In accordance with the present invention, a method has been  
discovered to produce certain aminocyanopyridine compounds that can  
inhibit the activity of MAPKAP kinase-2. These compounds can exhibit  
their inhibitory effect at low concentrations -- having *in vitro* MK-2 inhibition  
IC<sub>50</sub> values of under 1.0 μM, and with some having IC<sub>50</sub> values of under  
20 about 0.5 μM, and even as low as about 0.2 μM.

[00017] It has been discovered that these compounds can be produced  
by reacting a substituted benzaldehyde having the structure:

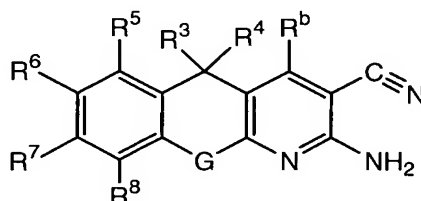


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with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



5 wherein:

Z is selected from the group consisting of -OH, -SH, and -NR<sup>a</sup>Y;

R<sub>a</sub> is selected from the group consisting of alkyl, aryl, and heteroaryl;

10 Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, it has no substituent groups;

15 when G is sulfur, it is either unsubstituted, or is substituted with one or two oxo groups;

when G is nitrogen, it is substituted with C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>b</sup> is selected from the group consisting of furyl and -NH-R<sup>2</sup>;

20 R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted

heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;  
and

$R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are each independently selected from the group  
consisting of:

5 hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  
 $C_1$ - $C_6$  alkoxy, hydroxy  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy  $C_1$ -  
 $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenoxy,

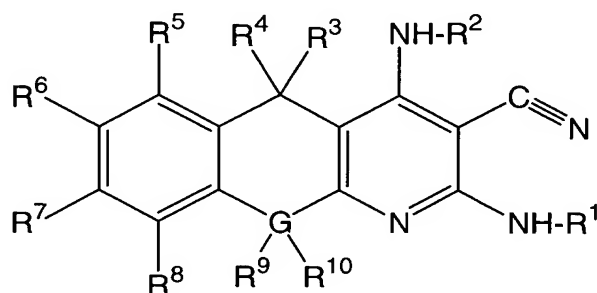
10 branched or unbranched amino  $C_1$ - $C_6$  alkyl, diamino  $C_2$ - $C_6$  alkyl,  $C_1$ -  
 $C_6$  alkylamino  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino, di-( $C_1$ - $C_6$  alkyl)amino,  $C_1$ - $C_4$   
alkoxyarylamino,  $C_1$ - $C_4$  alkoxyalkylamino, amino  $C_1$ - $C_6$  alkoxy, di-( $C_1$ - $C_4$   
alkylamino,  $C_2$ - $C_6$  alkoxy, di-( $C_1$ - $C_6$  alkyl)amino  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$   
alkylamino  $C_1$ - $C_6$  alkoxy, halo  $C_1$ - $C_6$  alkoxy, dihalo  $C_1$ - $C_6$  alkoxy, trihalo  $C_1$ -  
 $C_6$  alkoxy, cyano  $C_1$ - $C_6$  alkyl, dicyano  $C_1$ - $C_6$  alkyl, cyano  $C_1$ - $C_6$  alkoxy,  
15 dicyano  $C_1$ - $C_6$  alkoxy, carbamyl  $C_1$ - $C_4$  alkoxy, heterocyclyl  $C_1$ - $C_4$  alkoxy,  
heteroaryl  $C_1$ - $C_4$  alkoxy, sulfo, sulfamyl,  $C_1$ - $C_4$  alkylaminosulfonyl, hydroxy  
 $C_1$ - $C_4$  alkylaminosulfonyl, di-( $C_1$ - $C_4$  alkyl)aminosulfonyl,  $C_1$ - $C_4$  alkylthio,  $C_1$ -  
 $C_4$  alkylsulfonyl,  $C_1$ - $C_4$  alkylsulfinyl,

20 aryl, aryl  $C_1$ - $C_6$  alkyl, heterocyclyl  $C_1$ - $C_6$  alkyl, heteroaryl  $C_1$ - $C_6$  alkyl,  
heterocyclyl  $C_1$ - $C_6$  alkoxy, heteroaryl  $C_1$ - $C_6$  alkoxy, aryl  $C_1$ - $C_6$  alkoxy,  
where the aryl ring can be substituted or unsubstituted, and, if substituted,  
the substituent group is selected from one or more of the group consisting  
of  $C_1$ - $C_6$  alkyl, halo, amino, and  $C_1$ - $C_6$  alkoxy,

25 substituted or unsubstituted  $C_3$ - $C_6$  cyclyl,  $C_3$ - $C_6$  heterocyclyl, and, if  
substituted, the substituent group is selected from one or more of the  
group consisting of  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, halo, amino, and where the  
 $C_3$ - $C_6$  heterocyclyl ring contains O, S, or N,

30 branched or unbranched  $C_1$ - $C_6$  alkoxycarbonyl  $C_1$ - $C_6$  alkoxy, and  
carboxy, carboxy  $C_1$ - $C_6$  alkoxy, carboxy  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_4$   
alkoxycarbonyl,  $C_1$ - $C_4$  alkoxycarbonyl.

**[00018]** Aminocyanopyridine compounds that can be produced by the present method include those aminocyanopyridine compounds having the structure shown in formula I:



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wherein:

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  each is independently selected from the group consisting of

hydrogen, hydroxy, amino, halo, nitro,

10

branched or unbranched  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl,  $C_1$ - $C_6$  alkoxy, hydroxy  $C_1$ - $C_6$  alkyl, hydroxy  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkoxy  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkenoxy,

15

branched or unbranched amino  $C_1$ - $C_6$  alkyl, diamino  $C_2$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino, di-( $C_1$ - $C_6$  alkyl)amino,  $C_1$ - $C_4$  alkoxyarylamino,  $C_1$ - $C_4$  alkoxyalkylamino, amino  $C_1$ - $C_6$  alkoxy, di-( $C_1$ - $C_4$  alkylamino,  $C_2$ - $C_6$  alkoxy, di-( $C_1$ - $C_6$  alkyl)amino  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylamino  $C_1$ - $C_6$  alkoxy, halo  $C_1$ - $C_6$  alkoxy, dihalo  $C_1$ - $C_6$  alkoxy, trihalo  $C_1$ - $C_6$  alkoxy, cyano  $C_1$ - $C_6$  alkyl, dicyano  $C_1$ - $C_6$  alkyl, cyano  $C_1$ - $C_6$  alkoxy, dicyano  $C_1$ - $C_6$  alkoxy, carbamyl  $C_1$ - $C_4$  alkoxy, heterocyclyl  $C_1$ - $C_4$  alkoxy, heteroaryl  $C_1$ - $C_4$  alkoxy, sulfo, sulfamyl,  $C_1$ - $C_4$  alkylaminosulfonyl, hydroxy  $C_1$ - $C_4$  alkylaminosulfonyl, di-( $C_1$ - $C_4$  alkyl)aminosulfonyl,  $C_1$ - $C_4$  alkylthio,  $C_1$ - $C_4$  alkylsulfonyl,  $C_1$ - $C_4$  alkylsulfinyl,

20

aryl, aryl  $C_1$ - $C_6$  alkyl, heterocyclyl  $C_1$ - $C_6$  alkyl, heteroaryl  $C_1$ - $C_6$  alkyl, heterocyclyl  $C_1$ - $C_6$  alkoxy, heteroaryl  $C_1$ - $C_6$  alkoxy, aryl  $C_1$ - $C_6$  alkoxy, where the aryl ring can be substituted or unsubstituted, and, if substituted,

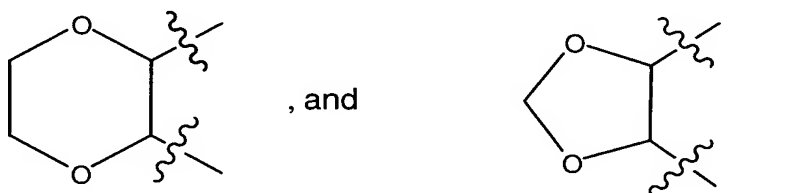
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the substituent group is selected from one or more of the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, halo, amino, and C<sub>1</sub>-C<sub>6</sub> alkoxy,

substituted or unsubstituted C<sub>3</sub>-C<sub>6</sub> cyclyl, C<sub>3</sub>-C<sub>6</sub> heterocyclyl, and, if substituted, the substituent group is selected from one or more of the group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, amino, and where the C<sub>3</sub>-C<sub>6</sub> heterocyclyl ring contains O, S, or N,

branched or unbranched C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkoxy, and carboxy, carboxy C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl,

where R<sup>6</sup> and R<sup>7</sup> are such that they can join to form a ring system of the type selected from



**[00019]** As shown above, ring substituent groups that join to form additional ring structures adjacent the substituted ring can be described with reference to chemical formulas that show wavy lines to indicate that a partial molecule is shown. In these formulas, the wavy lines cut through the ring to which the substituents are joined (in this case, the phenyl ring of formula I), rather than across the bond joining the substituent group to the ring. Accordingly, the partial ring that is shown is the ring to which the substituent groups are shown as being bonded in the general formula.

**[00020]** G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R<sup>9</sup> and R<sup>10</sup> are absent;

when G is sulfur, each of R<sup>9</sup> and R<sup>10</sup> is optionally absent or is oxo;

when G is nitrogen, R<sup>9</sup> is absent and R<sup>10</sup> is C<sub>1</sub>-C<sub>4</sub>-alkyl.

**[00021]** As used herein, the term "alkyl", alone or in combination, means an acyclic alkyl radical, linear or branched, which, unless otherwise noted, preferably contains from 1 to about 10 carbon atoms and more

preferably contains from 1 to about 6 carbon atoms. "Alkyl" also encompasses cyclic alkyl radicals containing from 3 to about 7 carbon atoms, preferably from 3 to 5 carbon atoms. The alkyl radicals can be optionally substituted with groups as defined below. Examples of such alkyl radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl, and the like.

**[00022]** The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. Unless otherwise noted, such radicals preferably contain from 2 to about 6 carbon atoms, preferably from 2 to about 4 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

**[00023]** The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups as described below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

**[00024]** The term "alkoxy" includes linear or branched oxy-containing radicals, each of which has, unless otherwise noted, alkyl portions of 1 to about 6 carbon atoms, preferably 1 to about 4 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, isobutoxy radicals, and the like.

**[00025]** The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form

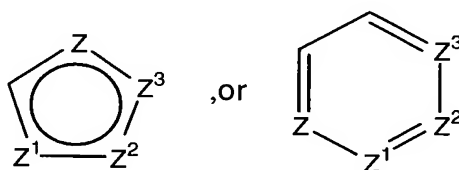
monoalkoxyalkyl and dialkoxyalkyl radicals. Examples of such radicals include methoxyalkyls, ethoxyalkyls, propoxyalkyls, isopropoxyalkyls, butoxyalkyls, tert-butoxyalkyls, and the like. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, fluoropropoxy, and the like.

**[00026]** The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, preferably, unless otherwise noted, of from 1 to about 6 carbon atoms, attached to a divalent sulfur atom. An example of "lower alkylthio", is methylthio ( $\text{CH}_3\text{-S-}$ ).

**[00027]** The term "alkylthioalkyl" embraces alkylthio radicals, attached to an alkyl group. An example of such radicals is methylthiomethyl.

**[00028]** The term "halo" means radicals comprising halogens, such as fluorine, chlorine, bromine, or iodine.

**[00029]** The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms is replaced by N, S, P, or O. This includes, for example, structures such as:



where Z,  $Z^1$ ,  $Z^2$ , or  $Z^3$  is C, S, P, O, or N, with the proviso that one of Z,  $Z^1$ ,  $Z^2$ , or  $Z^3$  is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z,  $Z^1$ ,  $Z^2$ , or  $Z^3$  only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.



**[00030]** The term "heteroaryl" means a fully unsaturated heterocycle, which can include, but is not limited to, furyl, thenyl, pyrrol, imidazolyl, pyrazolyl, pyridyl, thiazolyl, quinolinyl, isoquinolinyl, benzothienyl, and indolyl.

5 **[00031]** In either, "heterocyclyl" or "heteroaryl", the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.

**[00032]** The term "cycloalkyl" means a mono- or multi-ringed carbocycle wherein each ring contains three to about seven carbon atoms, preferably  
10 three to about six carbon atoms, and more preferably three to about five carbon atoms. Examples include radicals, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkenyl, and cycloheptyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered  
15 heterocyclic ring of the benzothiepine.

**[00033]** The term "oxo" means a doubly-bonded oxygen.

**[00034]** The term "aryl" means a fully unsaturated mono- or multi-ring carbocycle, including, but not limited to, substituted or unsubstituted phenyl, naphthyl, or anthracenyl.

20 **[00035]** The present aminocyanopyridine compounds inhibit the activity of the MK-2 enzyme. When it is said that a subject compound inhibits MK-2, it is meant that the MK-2 enzymatic activity is lower in the presence of the compound than it is under the same conditions in the absence of such compound.

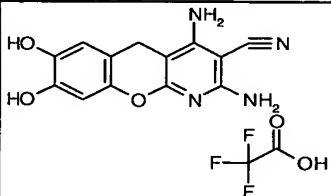
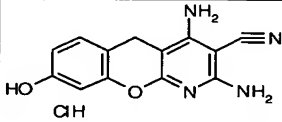
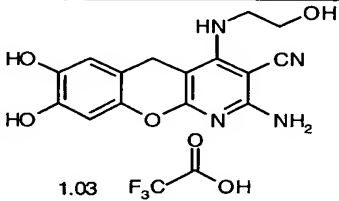
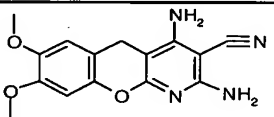
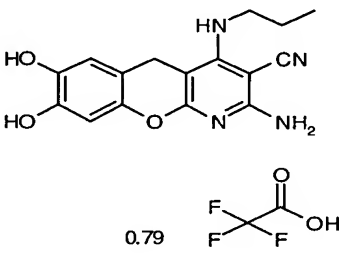
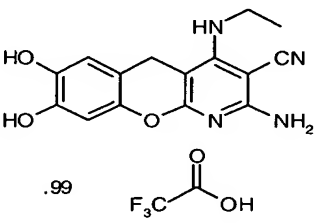
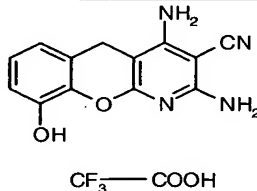
25 **[00036]** One method of expressing the potency of a compound as an MK-2 inhibitor is to measure the "IC<sub>50</sub>" value of the compound. The IC<sub>50</sub> value of an MK-2 inhibitor is the concentration of the compound that is required to decrease the MK-2 enzymatic activity by one-half.  
Accordingly, a compound having a lower IC<sub>50</sub> value is considered to be a  
30 more potent inhibitor than a compound having a higher IC<sub>50</sub> value. As used herein, aminocyanopyridine compounds that inhibit MK-2 can be

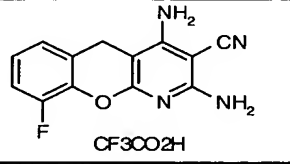
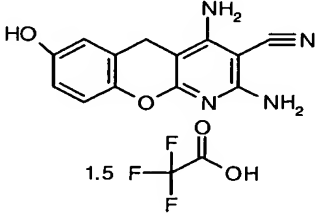
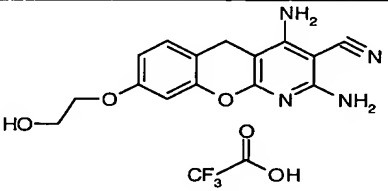
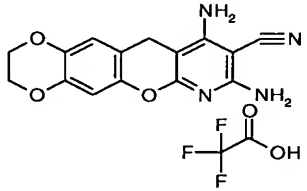
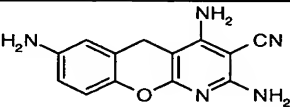
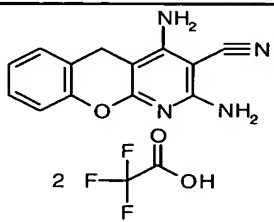
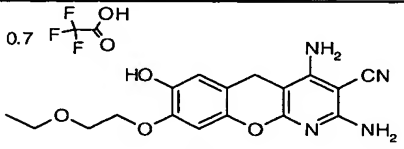
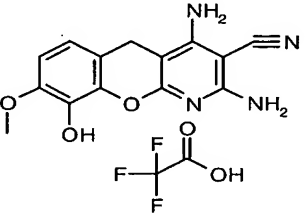
referred to as aminocyanopyridine MK-2 inhibitors, or aminocyanopyridine MK-2 inhibiting compounds or MK-2 inhibiting agents.

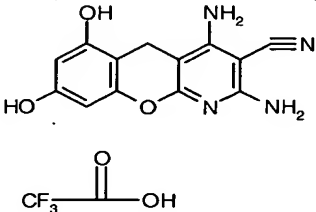
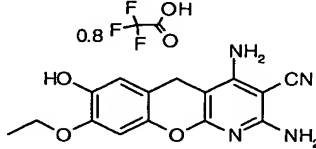
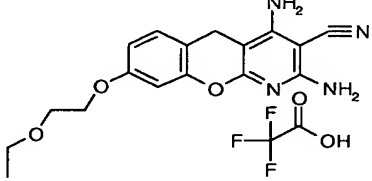
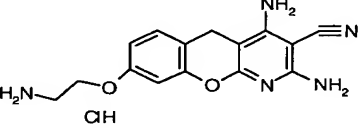
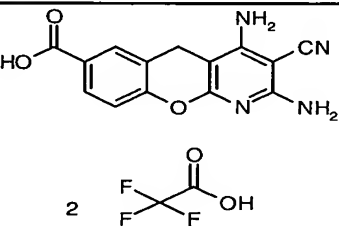
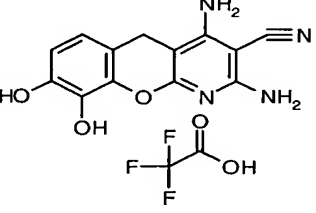
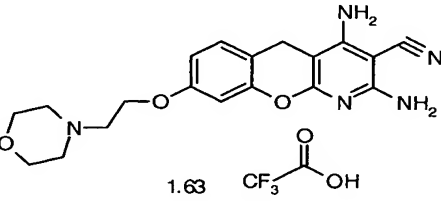
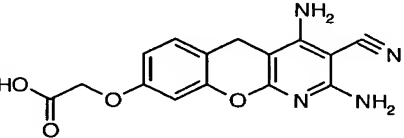
5 [00037] The tricyclic aminocyanopyridine compounds that are produced in the present invention include benzonaphthyridines, pyridochromanes, and pyridothiochromanes.

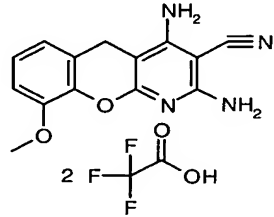
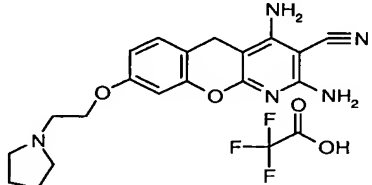
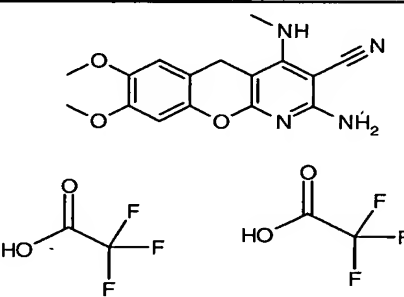
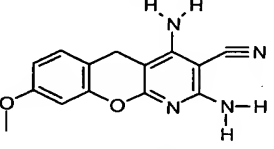
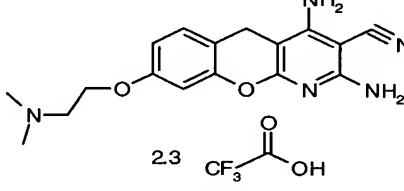
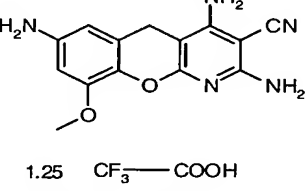
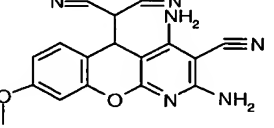
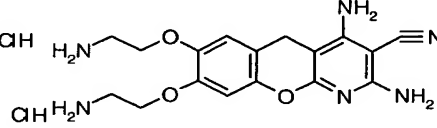
[00038] Examples of tricyclic aminocyanopyridine MK-2 inhibitors that can be produced by the present method are shown in Table I:

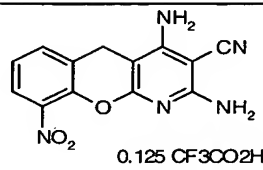
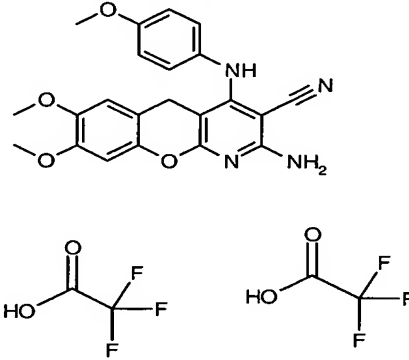
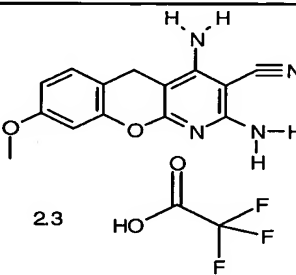
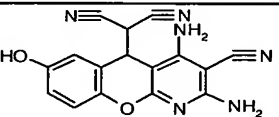
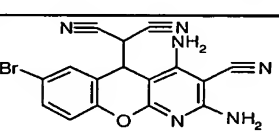
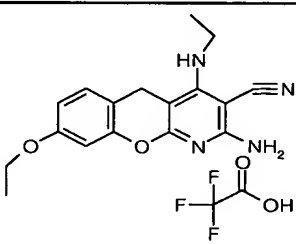
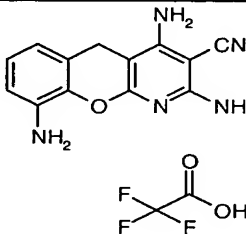
**Table I: Aminocyanopyridine MK-2 Inhibitors**

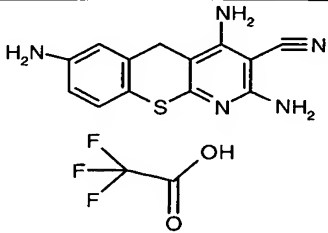
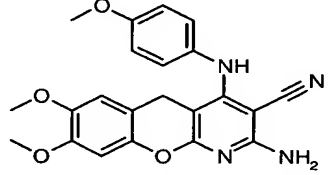
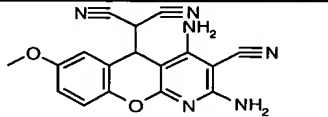
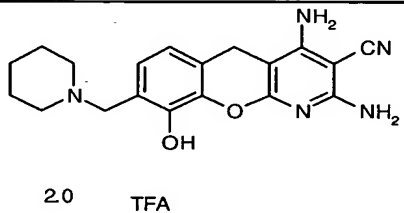
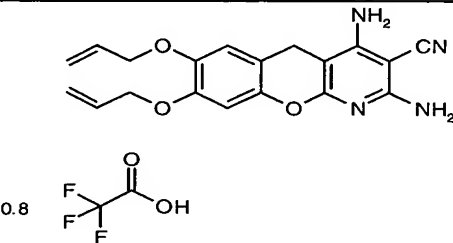
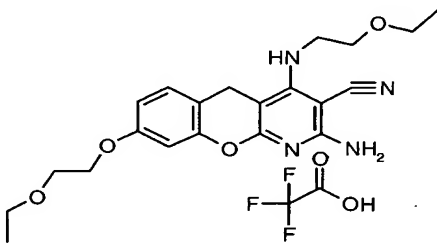
No.	Structure <sup>a</sup>	Compound Name(s) <sup>b</sup>	MK-2 Avg. IC50 (uM)
1		2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.125
2		2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile hydrochloride	0.187
3		2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.237
4		2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.335
5		2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.403
6		2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.419
7		2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.459

8	 CF <sub>3</sub> CO <sub>2</sub> H	2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.471
9	 1.5 F-CF <sub>2</sub> -COOH	2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.473
10	 CF <sub>3</sub> -COOH	2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.483
11	 F-CF <sub>2</sub> -COOH	8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile trifluoroacetate	0.488
12		2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.514
13	 2 F-CF <sub>2</sub> -COOH	2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.563
14	 0.7 F-CF <sub>2</sub> -COOH	2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.62
15	 F-CF <sub>2</sub> -COOH	2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.682

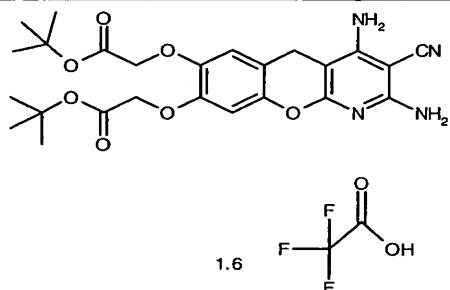
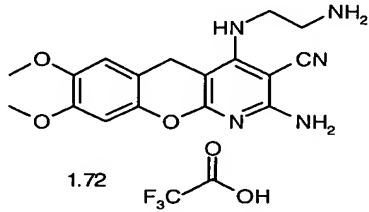
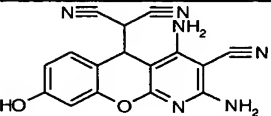
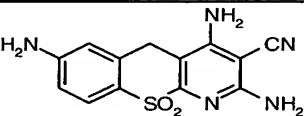
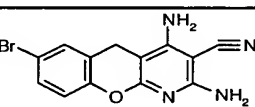
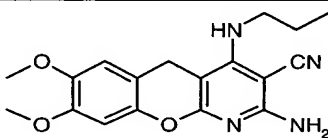
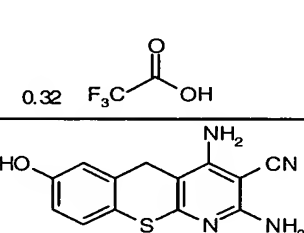
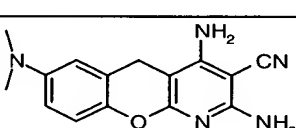
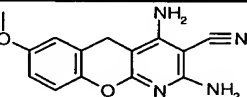
16		2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.694
17		2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.773
18		2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	0.817
19		2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile hydrochloride	0.82
20		2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid trifluoroacetate	0.857
21		2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.857
22		2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	0.91
23		[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid trifluoroacetate	0.916

24		2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.37
25		2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	1.68
26		2-amino-7,8-dimethoxy-4-(methylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	1.69
27		2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	1.72
28		2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.75
29		2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	1.79
30		2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	1.94
31		2,4-diamino-7,8-di[2-(amino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	2.55

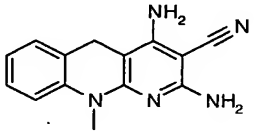
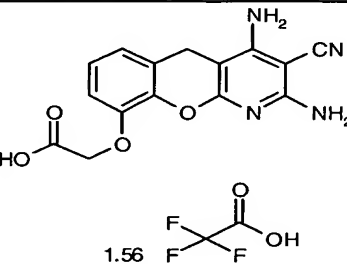
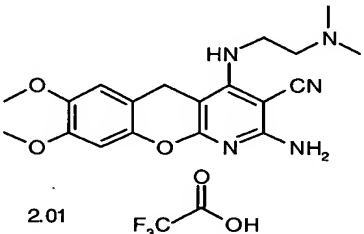
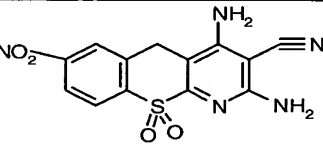
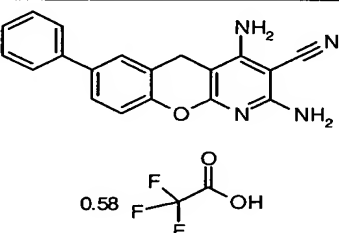
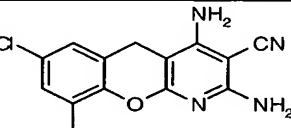
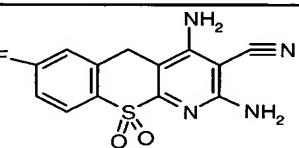
32	 <p>0.125 CF<sub>3</sub>CO<sub>2</sub>H</p>	2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	2.58
33		2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	2.98
34	 <p>2.3</p>	2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	3.24
35		2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	3.8
36		2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	4.22
37		2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	4.76
38		2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	5.01

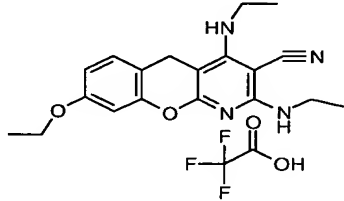

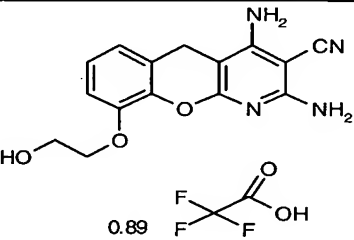
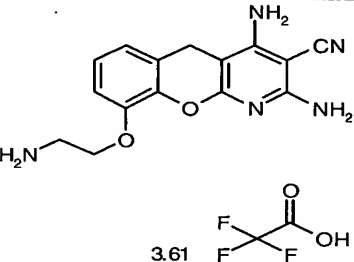
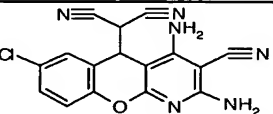
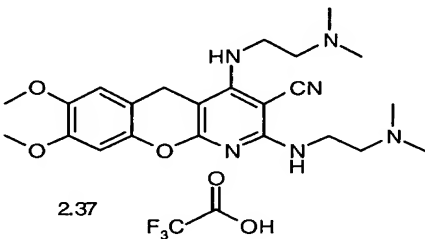
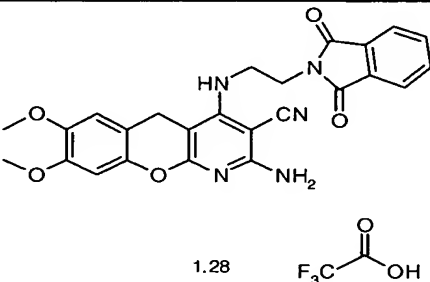
39		2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	5.6
40		2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	6.11
41		2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	6.18
42	 <p>2.0 TFA</p>	2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	8.28
43	 <p>0.8</p>	7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	9.6
44		2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	9.66

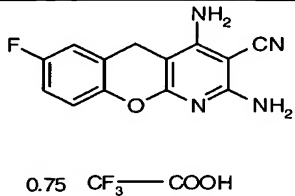
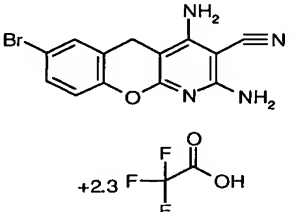
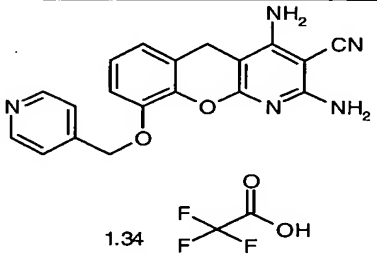
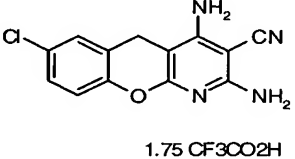
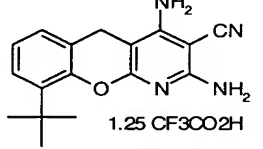
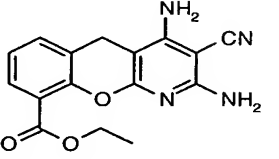
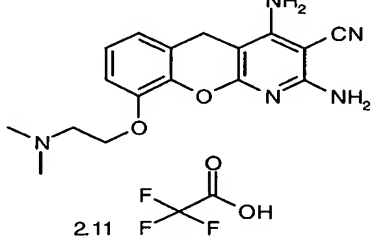


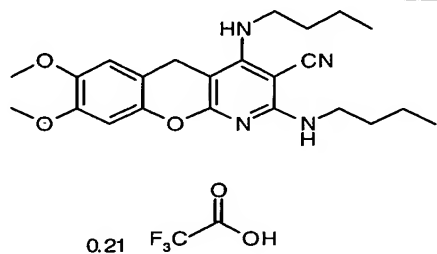
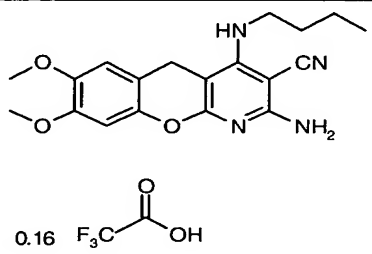
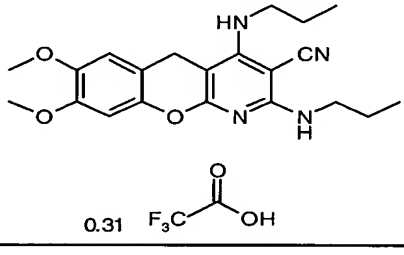
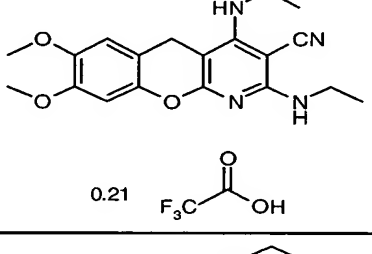
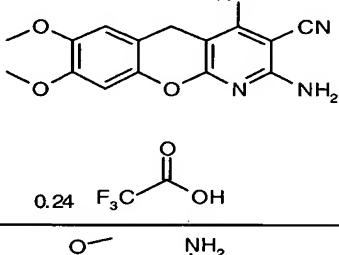
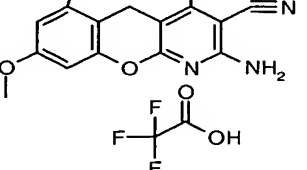
45		tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate trifluoroacetate	10.3
46		2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	11.5
47		2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	12.8
48		2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	14.4
49		2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	15.1
50		2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	15.6
51		2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile	17.4
52		2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	17.6
53		2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	19.7

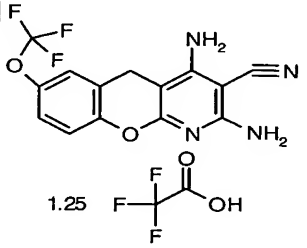
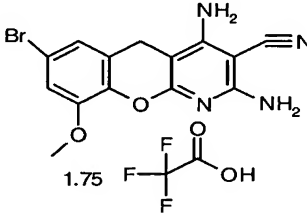
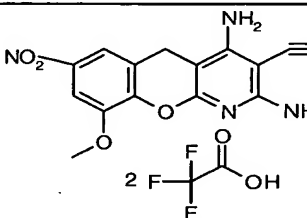
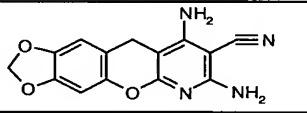
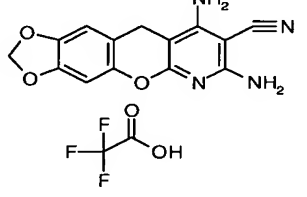
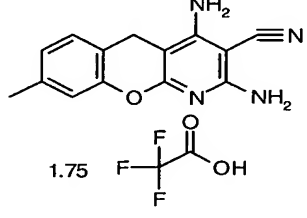
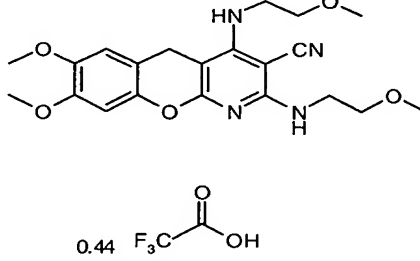
54		2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	21.2
55		2-amino-4-(benzylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	27.4
56		8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	33.8
57		2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	42.2
58		2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	43
59		2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	45.2
60		2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	62.2

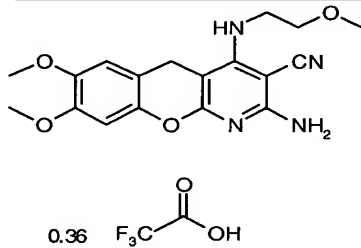
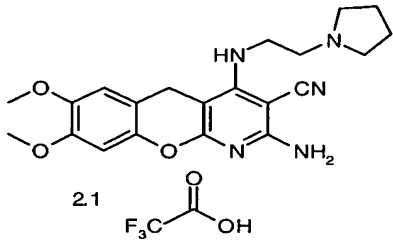
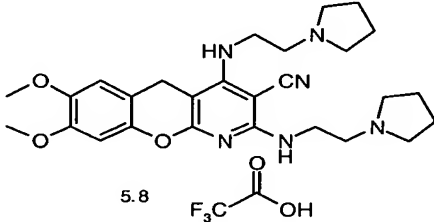
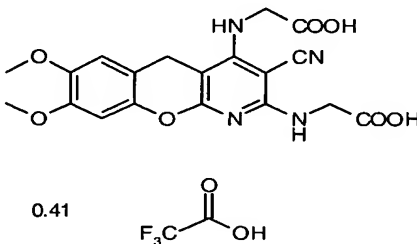
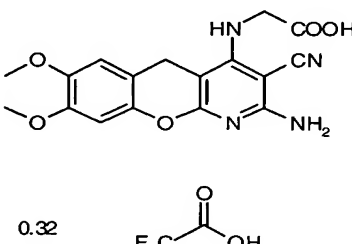
61	 <p>2.0 TFA</p>	2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate	70.1
62	 <p>1.56</p>	[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	72.2
63	 <p>2.01</p>	2-amino-4-[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	79.1
64		2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	80.8
65	 <p>0.58</p>	2,4-diamino-7-phenyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	83.8
66		2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	136
67		2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	142

68		8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	148
69		2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	151
70		2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	154
71		2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	161
72		2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	200
73		2,4-bis{[2-(dimethylamino)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
74		2-amino-4-{[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino}-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

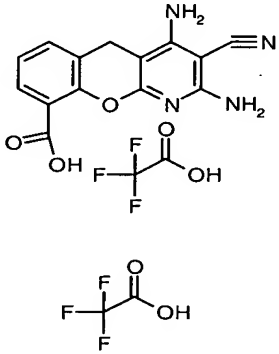
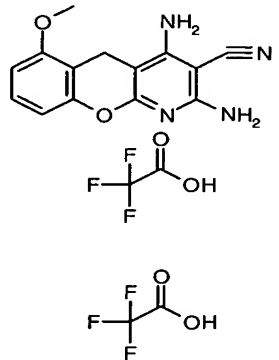
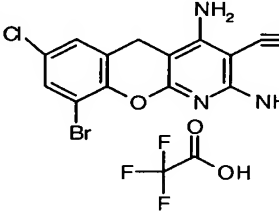
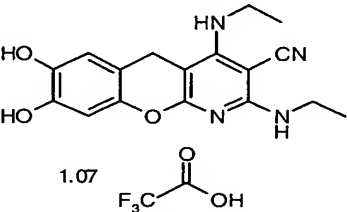
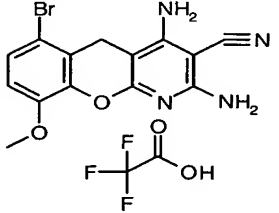
75	 <p>0.75 CF<sub>3</sub>—COOH</p>	2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
76	 <p>+2.3 F—C(=O)OH</p>	2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
77	 <p>1.34 F—C(=O)OH</p>	2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
78	 <p>1.75 CF<sub>3</sub>CO<sub>2</sub>H</p>	2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
79	 <p>1.25 CF<sub>3</sub>CO<sub>2</sub>H</p>	2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
80		ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate	200
81	 <p>2.11 F—C(=O)OH</p>	2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

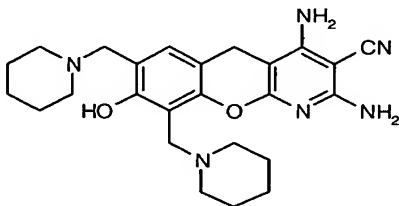
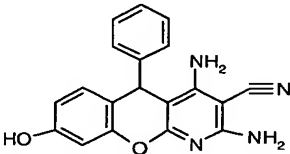
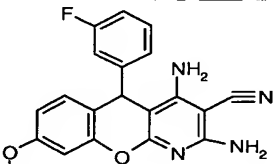
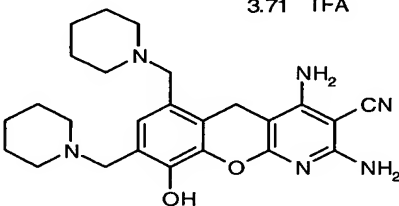
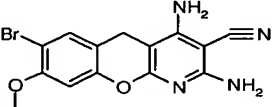
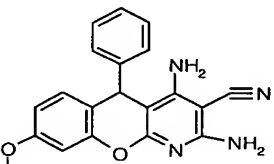
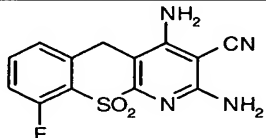
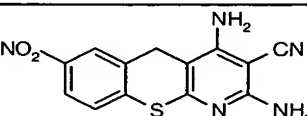
82		2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
83		2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
84		7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
85		2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
86		2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
87		2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

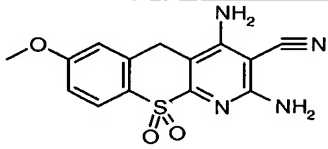
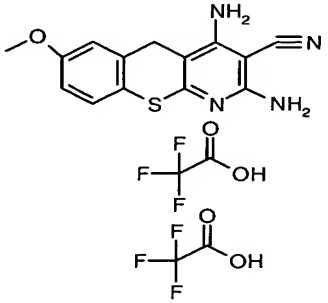
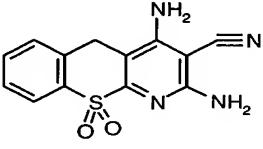
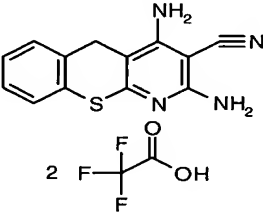
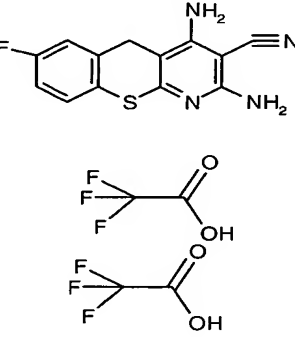
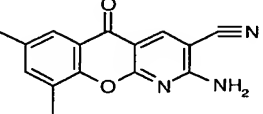
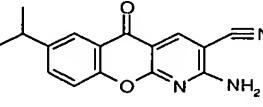
88	 <p>1.25</p>	2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
89	 <p>1.75</p>	2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
90	 <p>2</p>	2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
91		7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile	200
92	 <p>1</p>	7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile trifluoroacetate	200
93	 <p>1.75</p>	2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
94	 <p>0.44</p>	7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200

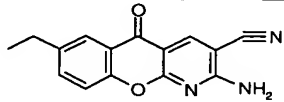
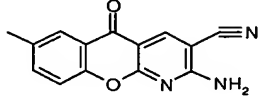
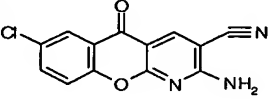
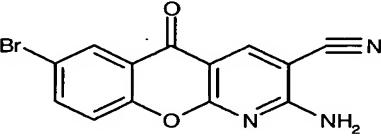
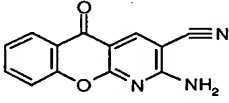
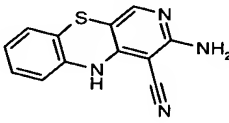
95	 <p>0.36 <math>\text{F}_3\text{C}-\text{COOH}</math></p>	2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
96	 <p>2.1 <math>\text{F}_3\text{C}-\text{COOH}</math></p>	2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
97	 <p>5.8 <math>\text{F}_3\text{C}-\text{COOH}</math></p>	7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
98	 <p>0.41 <math>\text{F}_3\text{C}-\text{COOH}</math></p>	2,4-bis(glycyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
99	 <p>0.32 <math>\text{F}_3\text{C}-\text{COOH}</math></p>	N-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine	200



100		2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid bis(trifluoroacetate)	200
101		2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
102		2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
103		2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
104		2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200

105	3.76 TFA 	2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
106		2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
107		2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
108	3.71 TFA 	2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
109		2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
110		2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
111		2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
112		2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile	200

113		2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
114		2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
115		2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	200
116		2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	200
117		2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	200
118		2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
119		2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200

120		2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
121		2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
122		2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
123		2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
124		2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	200
125		3-amino-5H-pyrido[3,4-b][1,4]benzothiazine-4-carbonitrile	200

**Notes:**

a: The aminocyanopyridine compound may be shown with a solvent, such as, for example, trifluoroacetate, with which it can form a salt. Both the salt and acid forms of the aminocyanopyridine compound are included in the present invention.

b: Compound names generated by ACD/Name software.

[00039] In another embodiment, the present method can produce aminocyanopyridine compounds having the structure shown in formula I, where:

5  $R^1$  is selected from the group consisting of hydrogen, branched or unbranched alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, arylalkyl, carboxy, carboxyalkyl, hydroxyalkyl, alkylcarboxy, aryl, amino, aminoalkyl, alkylamino, halo, alkylaminoalkyl, alkoxy, alkoxyalkyl, monocyclyl, bicyclyl, polycyclyl, and heterocyclyl;

10  $R^2$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

15  $R^3$  is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

$R^4$  is selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;

20  $R^5$  is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkyl, arylalkyl, or alkylaryl;

$R^6$  is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

25  $R^7$  is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclylalkyl, heterocyclylalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

30 where the  $R^6$  and  $R^7$  groups can join to form a six membered heterocyclic ring;

$R^8$  is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclylalkoxy, carboxyalkoxy,

pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclalkyl; and

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

- 5           when G is oxygen, R<sup>9</sup> and R<sup>10</sup> are absent;  
          when G is sulfur, each of R<sup>9</sup> and R<sup>10</sup> is optionally absent or is oxo;  
          when G is nitrogen, R<sup>9</sup> is absent and R<sup>10</sup> is C<sub>1</sub>-C<sub>4</sub>-alkyl.

**[00040]**   In another embodiment, the present method can be used to produce aminocyanopyridine compounds having the structure shown in  
10       formula I, where:

          R<sup>1</sup> is selected from the group consisting of hydrogen, ethyl, dimethylaminoethyl, butyl, propyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

15           R<sup>2</sup> is selected from the group consisting of hydrogen, hydroxyethyl, propyl, ethyl, methyl, 4-methoxyphenyl, ethoxyethyl, aminoethyl, phenylmethyl, dimethylaminoethyl, phthaloaminoethyl, butyl, methoxyethyl, tetramethylaminoethyl, and carboxymethyl;

          R<sup>3</sup> is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl.

20           R<sup>4</sup> is selected from the group consisting of hydrogen, dicyanomethyl, 2-fluorophenyl, phenyl, and 3-fluorophenyl;

          R<sup>5</sup> is selected from the group consisting of hydrogen, hydroxy, methoxy, bromo, and 2-pyridomethyl;

25           R<sup>6</sup> is selected from the group consisting of hydrogen, hydroxy, methoxy, amino, carboxy, diaminoethoxy, bromo, propoxy, isobutylcarboxymethoxy, dimethylamino, nitro, phenyl, chloro, pyridylmethyl, and fluoro;

30           R<sup>7</sup> is selected from the group consisting of hydrogen, hydroxy, methoxy, hydroxyethoxy, ethoxyethoxy, ethoxy, aminoethoxy, morpholinoethoxy, carboxymethoxy, *N*-pyrrolidylethoxy, dimethylaminoethoxy, pyridylmethyl, 2-propenoxy, and

isobutylcarboxymethoxy, where the R<sup>6</sup> and R<sup>7</sup> groups can join to form a six membered heterocyclic ring;

R<sup>8</sup> is selected from the group consisting of hydrogen, hydroxy, fluoro, methoxy, nitro, amino, pyrrolidylethoxy, carboxymethoxy, methyl, hydroxyethoxy, aminoethoxy, 4-pyridylmethoxy, isobutyl, ethylcarboxy, dimethylaminoethoxy, carboxy, bromo, and pyrridylmethyl; and

G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, R<sup>9</sup> and R<sup>10</sup> are absent;

when G is sulfur, each of R<sup>9</sup> and R<sup>10</sup> is optionally absent or is oxo;

when G is nitrogen, R<sup>9</sup> is absent and R<sup>10</sup> is -CH<sub>3</sub>.

**[00041]** In another embodiment, the present method can be used to produce aminocyanopyridine compounds that have an IC<sub>50</sub> of less than about 200 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R<sup>1</sup> is selected from the group consisting of hydrogen, and C<sub>1</sub>-C<sub>2</sub> alky;

R<sup>2</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>3</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxyphenyl, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>2</sub> alkyl, amino C<sub>1</sub>-C<sub>2</sub> alkyl, phenyl C<sub>1</sub>-C<sub>2</sub> alkyl, and di C<sub>1</sub>-C<sub>2</sub> alkylamino C<sub>1</sub>-C<sub>2</sub> alkyl;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, dicyano C<sub>1</sub>-C<sub>2</sub> alkyl, and halophenyl;

R<sup>5</sup> is selected from the group consisting of hydrogen, and hydroxy;

R<sup>6</sup> is selected from the group consisting of hydrogen, hydroxy, C<sub>1</sub> - C<sub>3</sub> alkoxy, amino, nitro, carboxy, diamino C<sub>1</sub> - C<sub>2</sub> alkoxy, halo, propenoxy, iso C<sub>3</sub> - C<sub>4</sub> alkylcarboxy C<sub>1</sub> - C<sub>2</sub> alkoxy, di C<sub>1</sub> - C<sub>2</sub> alkylamino, and phenyl;

R<sup>7</sup> is selected from the group consisting of hydrogen, hydroxy, C<sub>1</sub> - C<sub>3</sub> alkoxy, hydroxy C<sub>1</sub> - C<sub>2</sub> alkoxy, C<sub>1</sub> - C<sub>2</sub> alkoxy C<sub>1</sub> - C<sub>2</sub> alkoxy, amino C<sub>1</sub> - C<sub>2</sub> alkoxy, morpholino C<sub>1</sub> - C<sub>2</sub> alkoxy, carboxyl C<sub>1</sub> - C<sub>2</sub> alkoxy, pyrrolidyl C<sub>1</sub> - C<sub>2</sub> alkoxy, di C<sub>1</sub> - C<sub>2</sub> alkylamino C<sub>1</sub> - C<sub>2</sub> alkoxy, pyrrolidyl C<sub>1</sub> - C<sub>2</sub> alkyl, iso C<sub>3</sub> - C<sub>4</sub> alkylcarboxy C<sub>1</sub> - C<sub>2</sub> alkoxy, and 2-propenoxy,

where the R<sup>6</sup> and R<sup>7</sup> groups can join to form a six membered heterocyclic ring;

R<sup>8</sup> is selected from the group consisting of hydrogen, hydroxy, halo, C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy, nitro, amino, pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkoxy, carboxy C<sub>1</sub>-C<sub>2</sub> alkoxy, hydroxy C<sub>1</sub>-C<sub>2</sub> alkoxy, and amino C<sub>1</sub>-C<sub>2</sub> alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R<sup>9</sup> and R<sup>10</sup> is optionally absent or is oxo;

when G is oxygen, R<sup>9</sup> and R<sup>10</sup> are absent.

**[00042]** In another embodiment, the present method can be used to produce aminocyanopyridine compounds that have an IC<sub>50</sub> of less than about 100 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is selected from the group consisting of hydrogen, C<sub>1</sub> - C<sub>3</sub> alkyl, hydroxy C<sub>1</sub> - C<sub>2</sub> alkyl, C<sub>1</sub> - C<sub>2</sub> alkoxyphenyl, C<sub>1</sub> - C<sub>2</sub> alkoxy C<sub>1</sub> - C<sub>2</sub> alkyl, amino C<sub>1</sub> - C<sub>2</sub> alkyl, phenyl C<sub>1</sub> - C<sub>2</sub> alkyl, and di C<sub>1</sub> - C<sub>2</sub> alkylamino C<sub>1</sub> - C<sub>2</sub> alkyl;

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, and dicyano C<sub>1</sub> - C<sub>2</sub> alkyl.

R<sup>5</sup> is selected from the group consisting of hydrogen, and hydroxy;

R<sup>6</sup> is selected from the group consisting of hydrogen, hydroxy, C<sub>1</sub>-C<sub>2</sub> alkoxy, amino, carboxy, nitro, diamino C<sub>1</sub>-C<sub>2</sub> alkoxy, halo, 2-propenoxy, iso C<sub>3</sub>-C<sub>4</sub> alkylcarboxy C<sub>1</sub>-C<sub>2</sub> alkoxy, di C<sub>1</sub>-C<sub>2</sub> alkylamino, and phenyl;

R<sup>7</sup> is selected from the group consisting of hydrogen, hydroxy, C<sub>1</sub> - C<sub>2</sub> alkoxy, hydroxy C<sub>1</sub>-C<sub>2</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>2</sub> alkoxy, amino C<sub>1</sub>-C<sub>2</sub> alkoxy, morpholino C<sub>1</sub>-C<sub>2</sub> alkoxy, carboxyl C<sub>1</sub>-C<sub>2</sub> alkoxy, pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkoxy, di C<sub>1</sub>-C<sub>2</sub> alkylamino C<sub>1</sub>-C<sub>2</sub> alkoxy, pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkyl, iso C<sub>3</sub>-C<sub>4</sub> alkylcarboxy C<sub>1</sub>-C<sub>2</sub> alkoxy, and 2-propenoxy;

wherein the R<sup>6</sup> and R<sup>7</sup> groups can join to form a six membered heterocyclic ring;



R<sup>8</sup> is selected from the group consisting of hydrogen, hydroxy, halo, C<sub>1</sub>-C<sub>2</sub> alkoxy, nitro, amino, pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkoxy, and carboxy C<sub>1</sub>-C<sub>2</sub> alkoxy; and

G is selected from the group consisting of oxygen and sulfur;

5 when G is sulfur, each of R<sup>9</sup> and R<sup>10</sup> is optionally absent or is oxo;

when G is oxygen, R<sup>9</sup> and R<sup>10</sup> are absent.

**[00043]** In another embodiment, the present method can be used to produce aminocyanopyridine compounds having an IC<sub>50</sub> of less than about 50 μM, in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

10

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>3</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>2</sub> alkyl, C<sub>1</sub>-C<sub>2</sub> alkoxyphenyl, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>2</sub> alkyl, amino C<sub>1</sub>-C<sub>2</sub> alkyl, and phenyl C<sub>1</sub>-C<sub>2</sub> alkyl;

15

R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, and dicyano C<sub>1</sub>-C<sub>2</sub> alkyl.

R<sup>5</sup> is selected from the group consisting of hydrogen, and hydroxy;

20 R<sup>6</sup> is selected from the group consisting of hydrogen, hydroxy, C<sub>1</sub>-C<sub>2</sub> alkoxy, amino, carboxy, diamino C<sub>1</sub>-C<sub>2</sub> alkoxy, halo, 2-propenoxy, iso C<sub>3</sub>-C<sub>4</sub> alkylcarboxy C<sub>1</sub>-C<sub>2</sub> alkoxy, and di C<sub>1</sub>-C<sub>2</sub> alkylamino;

20

R<sup>7</sup> is selected from the group consisting of hydrogen, hydroxy, C<sub>1</sub>-C<sub>2</sub> alkoxy, hydroxy C<sub>1</sub>-C<sub>2</sub> alkoxy, C<sub>1</sub>-C<sub>2</sub> alkoxy C<sub>1</sub>-C<sub>2</sub> alkoxy, amino C<sub>1</sub>-C<sub>2</sub> alkoxy, morpholino C<sub>1</sub>-C<sub>2</sub> alkoxy, carboxyl C<sub>1</sub>-C<sub>2</sub> alkoxy, pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkoxy, di C<sub>1</sub>-C<sub>2</sub> alkylamino C<sub>1</sub>-C<sub>2</sub> alkoxy, pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkyl, iso C<sub>3</sub>-C<sub>4</sub> alkylcarboxy C<sub>1</sub>-C<sub>2</sub> alkoxy, and 2-propenoxy;

25

where the R<sup>6</sup> and R<sup>7</sup> groups can join to form a six membered heterocyclic ring;

R<sup>8</sup> is selected from the group consisting of hydrogen, hydroxy, halo, C<sub>1</sub>-C<sub>2</sub> alkoxy, nitro, amino, and pyrrolidyl C<sub>1</sub>-C<sub>2</sub> alkoxy; and

30

G is selected from the group consisting of oxygen and sulfur;

when G is sulfur, each of R<sup>9</sup> and R<sup>10</sup> is optionally absent or is oxo;

when G is oxygen, R<sup>9</sup> and R<sup>10</sup> are absent.

**[00044]** In another embodiment, the present method can be used to produce aminocyanopyridine compounds having an  $IC_{50}$  of less than about 20  $\mu M$ , in an *in vitro* assay of MK-2 inhibitory activity. Examples of such compounds comprise the compound shown in formula I, where:

5  $R^1$  is hydrogen;

$R^2$  is selected from the group consisting of hydrogen,  $C_1$ - $C_3$  alkyl, hydroxy  $C_1$ - $C_2$  alkyl,  $C_1$ - $C_2$  alkoxyphenyl,  $C_1$ - $C_2$  alkoxy  $C_1$ - $C_2$  alkyl, and amino  $C_1$ - $C_2$  alkyl;

10  $R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, and dicyanoethyl;

$R^5$  is selected from the group consisting of hydrogen, and hydroxy;

$R^6$  is selected from the group consisting of hydrogen, hydroxy,  $C_1$ - $C_2$  alkoxy, amino, carboxy, diamino  $C_1$ - $C_2$  alkoxy, halo, 2-propenoxy, iso  $C_3$ - $C_4$  alkylcarboxy  $C_1$ - $C_2$  alkoxy, and di  $C_1$ - $C_2$  alkylamino;

15  $R^7$  is selected from the group consisting of hydrogen, hydroxy,  $C_1$ - $C_2$  alkoxy, hydroxy  $C_1$ - $C_2$  alkoxy,  $C_1$ - $C_2$  alkoxy  $C_1$ - $C_2$  alkoxy, amino  $C_1$ - $C_2$  alkoxy, morpholino  $C_1$ - $C_2$  alkoxy, carboxyl  $C_1$ - $C_2$  alkoxy, pyrrolidyl  $C_1$ - $C_2$  alkoxy, di  $C_1$ - $C_2$  alkylamino  $C_1$ - $C_2$  alkoxy, pyrrolidyl  $C_1$ - $C_2$  alkyl, iso  $C_3$ - $C_4$  alkylcarboxy  $C_1$ - $C_2$  alkoxy, and 2-propenoxy;

20 where the  $R^6$  and  $R^7$  groups can join to form a six membered heterocyclic ring;

$R^8$  is selected from the group consisting of hydrogen, hydroxy, halo, methoxy, nitro, and amino; and

25 G is selected from the group consisting of oxygen and sulfur  
when G is sulfur, each of  $R^9$  and  $R^{10}$  is optionally absent or is oxo;  
when G is oxygen,  $R^9$  and  $R^{10}$  are absent.

**[00045]** Examples of aminocyanopyridine MK-2 inhibitor compounds that can be produced by the present invention include, without limitation, the following:

30 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

- 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-  
5 carbonitrile,  
2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-  
carbonitrile,  
2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
10 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-  
carbonitrile,  
8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-  
b]pyridine-9-carbonitrile,  
15 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile  
2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-  
carbonitrile,  
2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-  
20 carbonitrile,  
2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-  
carbonitrile,  
2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
25 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid,  
2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-  
carbonitrile,  
30 [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid,  
2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

- 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7,8-dimethoxy-4-(methylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
5 2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
10 2,4-diamino-7,8-di[2-(amino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
15 2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
20 2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,  
25 2-amino-7,8-dimethoxy-4-[(4-methoxyphenyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
30 7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

- 2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate,
- 5 2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,
- 10 2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,
- 15 2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
2-amino-4-(benzylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 20 8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 25 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile,  
[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,
- 30 2-amino-4-[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

- 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,  
2,4-diamino-7-phenyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
5 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,  
8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
10 2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile,  
15 2,4-bis[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-4-[[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
20 2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
25 ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate,  
2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
30 2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

- 7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 5 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 10 2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile,  
7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile,
- 15 2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 20 2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-bis(glyciny)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 25 *N*-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine,  
2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid,  
2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile,
- 30 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

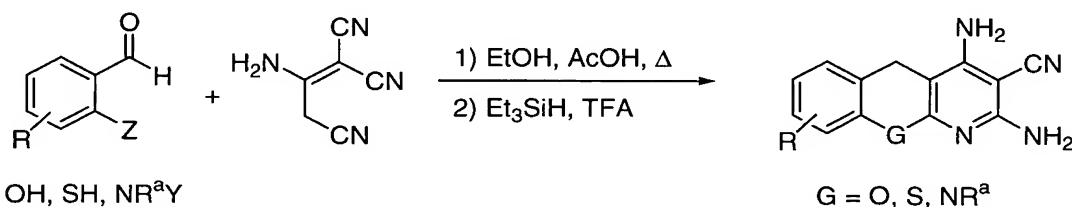
- 2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
5 2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
10 2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
15 2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,  
2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,  
20 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide,  
2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,  
2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7,9-dimethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
25 2-amino-7-isopropyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7-ethyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7-methyl-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7-chloro-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
2-amino-7-bromo-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile,  
30 2-amino-5-oxo-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and  
3-amino-5H-pyrido[3,4-b][1,4]benzothiazine-4-carbonitrile.



[00046] It should be understood that salts and prodrugs of the aminocyanopyridine compounds that are described herein, as well as isomeric forms, tautomers, racemic mixtures of the compounds, and the like, which have the same or similar activity as the compounds that are described, are to be considered to be included within the description of the compound.

[00047] Aminocyanopyridine MK-2 inhibiting compounds of the type shown in formula I, above, include tricyclic aminocyanopyridine MK-2 inhibiting compounds, such as benzonaphthyridines, pyridochromanes, and pyridothiochromanes. A general method for the synthesis of these tricyclic aminocyanopyridines is shown in Scheme 1, below:

Scheme 1:



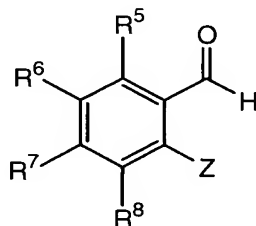
[00048] In this method, a substituted benzaldehyde is reacted with a tricarbonitrile, preferably 2-amino-1-propene-1,1,3-tricarbonitrile. The reaction can be carried out by heating the reactants to reflux in a solution of acetic acid and ethanol. The reaction product can be concentrated *in vacuo* and dissolved in trifluoroacetic acid. Triethylsilane is added and the mixture is stirred. In a preferred method, the mixture is stirred for about 1 hour at 0°C. Dichloromethane is then added and solids are collected. The solids can be collected by filtration, and can be washed with dichloromethane and ether. The solids comprise the desired tricyclic aminocyanopyridine MK-2 inhibiting compound of the type including benzonaphthyridines, pyridochromanes, and pyridothiochromanes.

[00049] Referring to the reactants and products shown above in Scheme I:

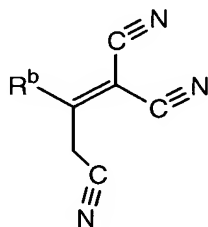
Z can be OH, SH, or  $\text{NR}^a\text{Y}$ , where Y is a protecting group for nitrogen. The Y group can be benzyl, allyl, an alkyl carbamate, or a benzyl carbamate. Other nitrogen protecting groups are known to persons having skill in the art of organic synthesis. A preferred protecting group is tert-butylcarbamate.  $\text{R}^a$  can be an alkyl group, an aryl group, or a heteroaryl group. The benzene ring of the benzaldehyde can be further substituted by one, two, three, or four additional R groups at carbons 3, 4, 5, or 6. Each R can independently be hydrogen; alkyl; aryl; a heteroatom, such as O, N, or S, substituted with hydrogen,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  branched alkyl, aryl, heteroaryl (wherein the heteroaryl can include, but is not limited to, pyrazolyl, imidazolyl, pyrrol, pyridyl, thiophyl, furyl and pyrimidyl), ester and amido.

**[00050]** Advantages of this method include that it is a general method that can be used to produce various types of the tricyclic compounds of formula I depending upon the types of reactants used. It is also an easy and straightforward synthesis method that can be carried out in a single vessel.

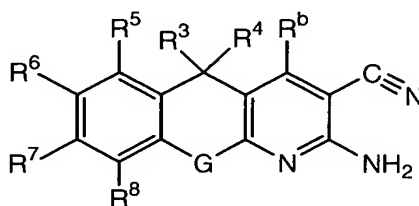
**[00051]** In an embodiment of this method of synthesis as described above, a tricyclic aminocyanopyridine MK-2 inhibiting compound can be prepared by reacting a substituted benzaldehyde having the structure:



with a tricarbonitrile having the structure:



to form an aminocyanopyridine compound having the structure:



5        wherein:

          Z is selected from the group consisting of -OH, -SH, and -NR<sup>a</sup>Y;

          R<sub>a</sub> is selected from the group consisting of alkyl, aryl, and  
heteroaryl;

10        Y is a protecting group for nitrogen. Examples of such nitrogen  
protecting groups include benzyl, allyl, alkyl carbamates and benzyl  
carbamates.

          G is selected from the group consisting of oxygen, sulfur, and  
nitrogen;

          when G is oxygen, it has no substituent groups;

15        when G is sulfur, it is either unsubstituted, or is substituted with one  
or two oxo groups;

          when G is nitrogen, it is substituted with C<sub>1</sub>-C<sub>4</sub> alkyl;

          R<sup>b</sup> is selected from the group consisting of furyl and -NH-R<sup>2</sup>;

20        R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, alkenyl,  
alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl,  
alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and  
carboxyalkyl;

25        R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group  
consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted  
heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties;  
and

          R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group  
consisting of hydrogen, hydroxy, alkoxy, halo, alkyl, alkenyl, alkyl,  
arylalkyl, alkylaryl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy,

aminoalkoxy, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylamino, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, heterocyclalkyl, heterocyclalkoxy, carboxyalkoxy, alkylaminoalkoxy, alkylcarboxyalkoxy, pyrrolidylethoxy, hydroxyalkoxy, and alkylcarboxy, where  $R^6$  and  $R^7$  are such that they optionally join to form a six membered heterocyclic ring.

**[00052]** In an embodiment of the general method described above,

$R^2$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

$R^3$  and  $R^4$  are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocycl and cycl, where substituents, if any, comprise halo moieties;

$R^5$  is selected from the group consisting of hydrogen, alkoxy, halo, alkyl, alkenyl, alkyl, arylalkyl, or alkylaryl;

$R^6$  is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkyl, alkenyl, alkynyl, amino, alkylamino, arylamino, alkylaminoalkyl, carboxy, aminoalkoxy, halo, alkylcarboxyalkyl, alkylamino, aminoalkyl, nitro, aryl, arylalkyl, alkylaryl, or arylamino;

$R^7$  is selected from the group consisting of hydrogen, hydroxy, alkoxy, alkenoxy, hydroxyalkoxy, alkoxyalkoxy, aminoalkoxy, heterocyclalkyl, heterocyclalkoxy, carboxyalkoxy, alkylaminoalkoxy, and alkylcarboxyalkoxy;

where the  $R^6$  and  $R^7$  groups can join to form a six membered heterocyclic ring; and

$R^8$  is selected from the group consisting of hydrogen, hydroxy, halo, nitro, amino, alkyl, alkoxy, heterocyclalkoxy, carboxyalkoxy, pyrrolidylethoxy, carboxymethoxy, hydroxyalkoxy, aminoalkoxy, alkylcarboxy, alkylaminoalkyl, carboxy, and heterocyclalkyl.

**[00053]** In a preferred embodiment of this method, the substituted benzaldehyde comprises salicaldehyde and the tricarbonitrile comprises 2-

amino-1-propene-1,1,3-tricarbonitrile. It is also preferred that the nitrogen protecting group "Y", comprises tert-butylcarbamate.

**[00054]** In an embodiment of the present method,

Z is selected from the group consisting of -OH, -SH, and -NR<sup>a</sup>Y;

5 R<sub>a</sub> is selected from the group consisting of alkyl, aryl, and heteroaryl;

Y is a protecting group for nitrogen that is selected from the group consisting of benzyl, allyl, alkyl carbamates and benzyl carbamate;

10 G is selected from the group consisting of oxygen, sulfur, and nitrogen;

when G is oxygen, it has no substituent groups;

when G is sulfur, it is either unsubstituted, or is substituted with one or two oxo groups;

when G is nitrogen, it is substituted with C<sub>1</sub>-C<sub>4</sub> alkyl;

15 R<sup>b</sup> is selected from the group consisting of furyl and -NH-R<sup>2</sup>;

R<sup>2</sup> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxyalkyl, alkylaryl, arylalkyl, alkoxyaryl, aminoalkyl, alkylaminoalkyl, arylaminoalkyl, alkoxyalkyl, alkylcarboxy, and carboxyalkyl;

20 R<sup>3</sup> and R<sup>4</sup> are each independently selected from the group consisting of hydrogen, dicyanoalkyl, and substituted or unsubstituted heterocyclyl and cyclyl, where substituents, if any, comprise halo moieties; and

25 R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are each independently selected from the group consisting of:

hydrogen, hydroxy, amino, halo, nitro,

branched or unbranched C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, hydroxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenoxy,

30 branched or unbranched amino C<sub>1</sub>-C<sub>6</sub> alkyl, diamino C<sub>2</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylamino C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylamino, di-(C<sub>1</sub>-C<sub>6</sub> alkyl)amino, C<sub>1</sub>-C<sub>4</sub> alkoxyarylamino, C<sub>1</sub>-C<sub>4</sub> alkoxyalkylamino, amino C<sub>1</sub>-C<sub>6</sub> alkoxy, di-(C<sub>1</sub>-C<sub>4</sub>

alkylamino, C<sub>2</sub>-C<sub>6</sub> alkoxy, di-(C<sub>1</sub>-C<sub>6</sub> alkyl)amino C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub>  
alkylamino C<sub>1</sub>-C<sub>6</sub> alkoxy, halo C<sub>1</sub>-C<sub>6</sub> alkoxy, dihalo C<sub>1</sub>-C<sub>6</sub> alkoxy, trihalo C<sub>1</sub>-  
C<sub>6</sub> alkoxy, cyano C<sub>1</sub>-C<sub>6</sub> alkyl, dicyano C<sub>1</sub>-C<sub>6</sub> alkyl, cyano C<sub>1</sub>-C<sub>6</sub> alkoxy,  
dicyano C<sub>1</sub>-C<sub>6</sub> alkoxy, carbamyl C<sub>1</sub>-C<sub>4</sub> alkoxy, heterocyclyl C<sub>1</sub>-C<sub>4</sub> alkoxy,  
5 heteroaryl C<sub>1</sub>-C<sub>4</sub> alkoxy, sulfo, sulfamyl, C<sub>1</sub>-C<sub>4</sub> alkylaminosulfonyl, hydroxy  
C<sub>1</sub>-C<sub>4</sub> alkylaminosulfonyl, di-(C<sub>1</sub>-C<sub>4</sub> alkyl)aminosulfonyl, C<sub>1</sub>-C<sub>4</sub> alkylthio, C<sub>1</sub>-  
C<sub>4</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,

aryl, aryl C<sub>1</sub>-C<sub>6</sub> alkyl, heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkyl, heteroaryl C<sub>1</sub>-C<sub>6</sub> alkyl,  
heterocyclyl C<sub>1</sub>-C<sub>6</sub> alkoxy, heteroaryl C<sub>1</sub>-C<sub>6</sub> alkoxy, aryl C<sub>1</sub>-C<sub>6</sub> alkoxy,  
10 where the aryl ring can be substituted or unsubstituted, and, if substituted,  
the substituent group is selected from one or more of the group consisting  
of C<sub>1</sub>-C<sub>6</sub> alkyl, halo, amino, and C<sub>1</sub>-C<sub>6</sub> alkoxy,

substituted or unsubstituted C<sub>3</sub>-C<sub>6</sub> cyclyl, C<sub>3</sub>-C<sub>6</sub> heterocyclyl, and, if  
substituted, the substituent group is selected from one or more of the  
15 group consisting of C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halo, amino, and where the  
C<sub>3</sub>-C<sub>6</sub> heterocyclyl ring contains O, S, or N,

branched or unbranched C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl C<sub>1</sub>-C<sub>6</sub> alkoxy, and  
carboxy, carboxy C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy C<sub>1</sub>-C<sub>4</sub>  
alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub> alkoxycarbonyl.

20 **[00055]** And where the terms "alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl,  
haloalkoxy, halo, alkylthio, alkylthioalkyl, heterocyclyl, cyclyl, aryl,  
heteroaryl, cycloaryl, and oxo" have the same meanings as described  
above.

**[00056]** Further details of the synthesis of aminocyanopyridines are  
25 provided in the examples.

**[00057]** The MK-2 inhibiting activity of an aminocyanopyridine  
compound can be determined by any one of several methods that are well  
known to those having skill in the art of enzyme activity testing. One such  
method is described in detail in the general methods section of the  
30 examples. In addition, the efficacy of an aminocyanopyridine MK-2  
inhibiting compound in therapeutic applications can be determined by  
testing for inhibition of TNF $\alpha$  production in cell culture and in animal model

assays. In general, it is preferred that the aminocyanopyridine MK-2 inhibiting compounds of the present invention be capable of inhibiting the production and/or the release of TNF $\alpha$  in cell cultures and in animal models.

5     **[00058]**     It should be recognized that the isomeric forms and tautomers and the pharmaceutically-acceptable salts of the aminocyanopyridine MK-2 inhibitors that are produced by the present method can be easily produced by simple additional reactions. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic,  
10     glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic,  
15     cyclohexylaminosulfonic, algenic,  $\beta$ -hydroxybutyric, galactaric and galacturonic acids.

**[00059]**     Suitable pharmaceutically-acceptable base addition salts that can be used with the compounds produced by the present invention include metallic ion salts and organic ion salts. More preferred metallic ion  
20     salts include, but are not limited to, appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary  
25     ammonium salts, including in part, trifluoroacetate, trimethylamine, diethylamine, *N,N*-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present  
30     invention.

**[00060]**     The tricyclic aminocyanopyridine compounds that can be produced by the present invention are useful for, but not limited to, the

prevention and treatment of diseases and disorders that are mediated by  $\text{TNF}\alpha$ . For example, the aminocyanopyridine MK-2 inhibitors of the invention would be useful to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such aminocyanopyridine MK-2 inhibitor compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, and skin related conditions such as psoriasis, eczema, burns and dermatitis.

**[00061]** The tricyclic aminocyanopyridine MK-2 inhibitor compounds that can be produced by the present method also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Such aminocyanopyridine MK-2 inhibiting compounds would be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

**[00062]** The tricyclic aminocyanopyridine MK-2 inhibitors would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. These compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the



treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease.

**[00063]** The following examples describe preferred embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples all percentages are given on a weight basis unless otherwise indicated.

GENERAL INFORMATION FOR PREPARATION METHODS:

**[00064]** Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

**[00065]** NMR analysis:

**[00066]** Proton nuclear magnetic resonance spectra were obtained on a Varian Unity Innova 400, a Varian Unity Innova 300 a Varian Unity 300, a Bruker AMX 500 or a Bruker AV-300 spectrometer. Chemical shifts are given in ppm ( $\delta$ ) and coupling constants,  $J$ , are reported in Hertz.

Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra.

Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer, a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer, a PerSeptive Biosystems Mariner TOF HPLC-MS (ESI), or a Waters ZQ mass spectrometer (ESI).

**[00067]** Determination of MK-2  $IC_{50}$ :

**[00068]** Recombinant MAPKAPK2 was phosphorylated at a concentration of 42-78  $\mu$ M by incubation with

0.23  $\mu$ M of active p38 $\alpha$  in 50 mM HEPES, 0.1 mM EDTA, 10 mM magnesium acetate, and 0.25 mM ATP, pH 7.5 for one hour at 30°C.

**[00069]** The phosphorylation of HSP-peptide (KKKALSRQLSVAA) by MAPKAPK2 was measured using an anion exchange resin capture assay

method. The reaction was carried out in 50 mM  $\beta$ -glycerolphosphate, 0.04 % BSA, 10 mM magnesium acetate, 2% DMSO and 0.8 mM dithiotheritol, pH 7.5 in the presence of the HSP-peptide with 0.2  $\mu$ Ci [ $\gamma^{33}$ P]ATP and 0.03mM ATP. The reaction was initiated by the addition of 15 nM

5 MAPKAPK2 and was allowed to incubate at 30°C for 30 min. The reaction was terminated and [ $\gamma^{33}$ P]ATP was removed from solution by the addition of 150  $\mu$ l of AG 1X8 ion exchange resin in 900 mM sodium formate pH 3.0.

A 50  $\mu$ l aliquot of head volume was removed from the quenched reaction mixture and added to a 96-well plate, 150  $\mu$ l of Microscint-40 (Packard) was added and the amount of phosphorylated-peptide was determined. Allow the Microscint to sit in the plates for 60 minutes prior to counting.

10 **[00070]** Compounds are evaluated as potential inhibitors of the MK2 kinase by measuring their effects on MK2 phosphorylation of the peptide substrate. Compounds may be screened initially at two concentrations prior to determination of IC<sub>50</sub> values. Screening results are expressed as percent inhibition at the concentrations of compound tested. For IC<sub>50</sub> value determinations, compounds are tested at six concentrations in ten-fold serial dilutions with each concentration tested in triplicate. Results are expressed as IC<sub>50</sub> values in micromolar. The assay is performed at a final  
15 concentration of 2% DMSO.

20 **[00071]** Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention provide IC<sub>50</sub> values for MK-2 inhibition of below 200  $\mu$ M. One method that can be used for determining the MK-2 inhibition IC<sub>50</sub> value is that described just above. More preferred aminocyanopyridine  
25 MK-2 inhibiting compounds have the capability of providing MK-2 inhibition IC<sub>50</sub> values of below 100  $\mu$ M, yet more preferred of below 50  $\mu$ M, even more preferred of below 20  $\mu$ M, yet more preferred of below 10  $\mu$ M, and even more preferred of below 1 $\mu$ M.

**[00072]** U937 Cell TNF $\alpha$  release assay

30 **[00073]** The human monocyte-like cell line, U937 (ATCC #CRL-1593.2), is cultured in RPMI1640 media with 10% heat-inactivated fetal calf serum

(GIBCO), glutamine and pen/strep at 37°C and 5% CO<sub>2</sub>. Differentiation of U937 to monocytic/macrophage-like cells is induced by the addition of phorbol12-myristate 13-acetate (Sigma) at final concentration of 20 ng/ml to a culture of U937 cells at ~0.5 million cells/ml and incubated for 24 hrs.

5 The cells are centrifuged, washed with PBS and resuspended in fresh media without PMA and incubated for 24 hrs. Cells adherent to the culture flask are harvested by scraping, centrifugation, and resuspended in fresh media to 2 million cells/ml, and 0.2 ml is aliquoted to each of 96 wells in flat-bottom plate. Cells are then incubated for an additional 24 hrs to allow  
10 for recovery. The media is removed from the cells, and 0.1 ml of fresh media is added per well. 0.05 ml of serially diluted compound or control vehicle (Media with DMSO) is added to the cells. The final DMSO concentration does not exceed 1%. After 1hr incubation, 0.05 ml of 400ng/ml LPS (E Coli serotype 0111:B4, Sigma) in media is added for final  
15 concentration of 100 ng/ml. Cells are incubated at 37°C for 4 hrs. After 4 hrs incubation, supernatants are harvest and assayed by ELISA for the presence of TNF $\alpha$ .

**[00074] U937 cell TNF $\alpha$  ELISA**

**[00075]** ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface)  
20 were coated with purified mouse monoclonal IgG1 anti-human TNF $\alpha$  antibody (R&D Systems #MAB610; 1.25 ug/ml in sodium bicarbonate pH 8.0, 0.1 ml/well) and incubated at 4°C. Coating solution was aspirated the following day and wells were blocked with 1 mg/ml gelatin in PBS (plus 1x thimerasol) for 2 days at 4°C. Prior to using, wells were washed 3x with  
25 wash buffer (PBS with 0.05% Tween). Cultured media samples were diluted in EIA buffer (5 mg/ml bovine  $\gamma$ -globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS), added to wells (0.1 ml/well) in triplicate and allowed to incubate for 1.5 hr at 37°C in a humidified chamber. Plates were again washed and 0.1 ml/well of a mixture of rabbit  
30 anti-human TNF $\alpha$  polyclonal antibodies in EIA buffer (1:400 dilution of Sigma #T8300, and 1:400 dilution of Calbiochem #654250) was added for

1 hr at 37°C. Plates were washed as before and peroxidase-conjugated goat anti-rabbit IgG (H+L) antibody (Jackson ImmunoResearch #111-035-144, 1 ug/ml in EIA buffer, 0.1 ml/well) was added for 45 min. After final washing, plates were developed with peroxidase-ABTS solution

5 (Kirkegaard/Perry #50-66-01, 0.1 ml/well). Enzymatic conversion of ABTS to colored product was measured after 5-30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices) at 405 nm. TNF levels were quantitated from a recombinant human TNF $\alpha$  (R&D Systems #210-TA-010) standard curve using a quadratic parameter fit generated by  
10 SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. IC<sub>50</sub> values for compounds were generated using BioAssay Solver.

[00076] Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention provide TNF $\alpha$  release IC<sub>50</sub> values of below 200  $\mu$ M  
15 in an *in vitro* cell assay. One method that can be used for determining TNF $\alpha$  release IC<sub>50</sub> in an *in vitro* cell assay is that described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing TNF $\alpha$  release IC<sub>50</sub> values of below 50  $\mu$ M, yet more preferred of below 10, and even more preferred of below 1.0  $\mu$ M.

20 [00077] Lipopolysaccharide (LPS)-Induced TNF $\alpha$  Production.

[00078] Adult male 225-250 gram Lewis rats (Harlan Sprague-Dawley) were used. Rats were fasted 18 hr prior to oral dosing, and allowed free access to water throughout the experiment. Each treatment group consisted of 5 animals.

25 [00079] Compounds were prepared as a suspension in a vehicle consisting of 0.5% methylcellulose, 0.025% Tween-20 in PBS. Compounds or vehicle were orally administered in a volume of 1 ml using an 18 gauge gavage needle. LPS (*E. coli* serotype 0111:B4, Lot #39H4103, Cat. # L-2630, Sigma) was administered 1-4 hr later by  
30 injection into the penile vein at a dose of 1 mg/kg in 0.5 ml sterile saline. Blood was collected in serum separator tubes via cardiac puncture 1.5 hr

after LPS injection, a time point corresponding to maximal TNF $\alpha$  production. After clotting, serum was withdrawn and stored at -20°C until assay by ELISA (described below).

**[00080]    Rat LPS TNF $\alpha$  ELISA**

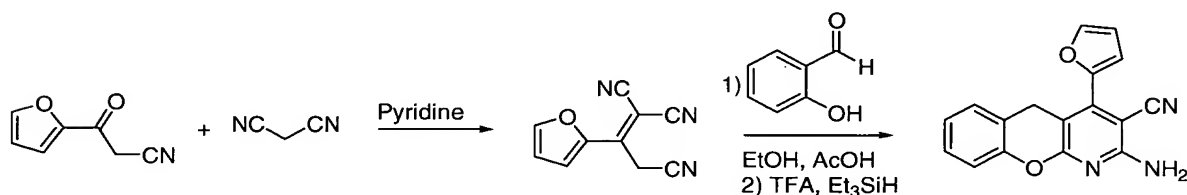
5    **[00081]**    ELISA plates (NUNC-Immuno™ Plate Maxisorb™ Surface) were coated with 0.1 ml per well of an Protein G purified fraction of a 2.5 ug/ml of hamster anti-mouse/rat TNF $\alpha$  monoclonal antibody TN19.12 (2.5 ug/ml in PBS, 0.1 ml/well). The hybridoma cell line was kindly provided by Dr. Robert Schreiber, Washington University. Wells were blocked the following day with 1 mg/ml gelatin in PBS. Serum samples were diluted in a buffer consisting of 5 mg/ml bovine  $\gamma$ -globulin, 1 mg/ml gelatin, 1 ml/l Tween-20, 1 mg/ml thimerasol in PBS, and 0.1 ml of diluted serum was added wells in duplicate and allowed to incubate for 2 hr at 37°C. Plates were washed with PBS-Tween, and 0.1 ml per well of a 1:300 dilution of rabbit anti-mouse/rat TNF $\alpha$  antibody (BioSource International, Cat. #AMC3012) was added for 1.5 hr at 37°C. Plates were washed, and a 1:1000 fold dilution of peroxidase-conjugated donkey anti-rabbit IgG antibody (Jackson ImmunoResearch, Cat. #711-035-152) was added for 45 min. After washing, plates were developed with 0.1 ml of ABTS-peroxide solution (Kirkegaard/Perry, Cat. #50-66-01). Enzymatic conversion of ABTS to colored product was measured after ~30 minutes using a SpectroMax 340 spectrophotometer (Molecular Devices Corp.) at 405 nm. TNF levels in serum were quantitated from a recombinant rat TNF $\alpha$  (BioSource International, Cat. #PRC3014.) standard curve using a quadratic parameter fit generated by SoftMaxPRO software. ELISA sensitivity was approximately 30 pg TNF/ml. Results are expressed in percent inhibition of the production of TNF $\alpha$  as compared to blood collected from control animals dosed only with vehicle.

25  
30    **[00082]**    Preferred aminocyanopyridine MK-2 inhibiting compounds of the present invention are capable of providing some degree of inhibition of TNF $\alpha$  in animals. That is, the degree of inhibition of TNF $\alpha$  in animals is

over 0%. One method for determining the degree of inhibition of TNF $\alpha$  is the rat LPS assay that is described just above. More preferred aminocyanopyridine MK-2 inhibiting compounds have the capability of providing rat LPS TNF $\alpha$  inhibition values of at least about 25%, even more preferred of above 50%, yet more preferred of above 70%, and even more preferred of above 80%.

#### EXAMPLE 1

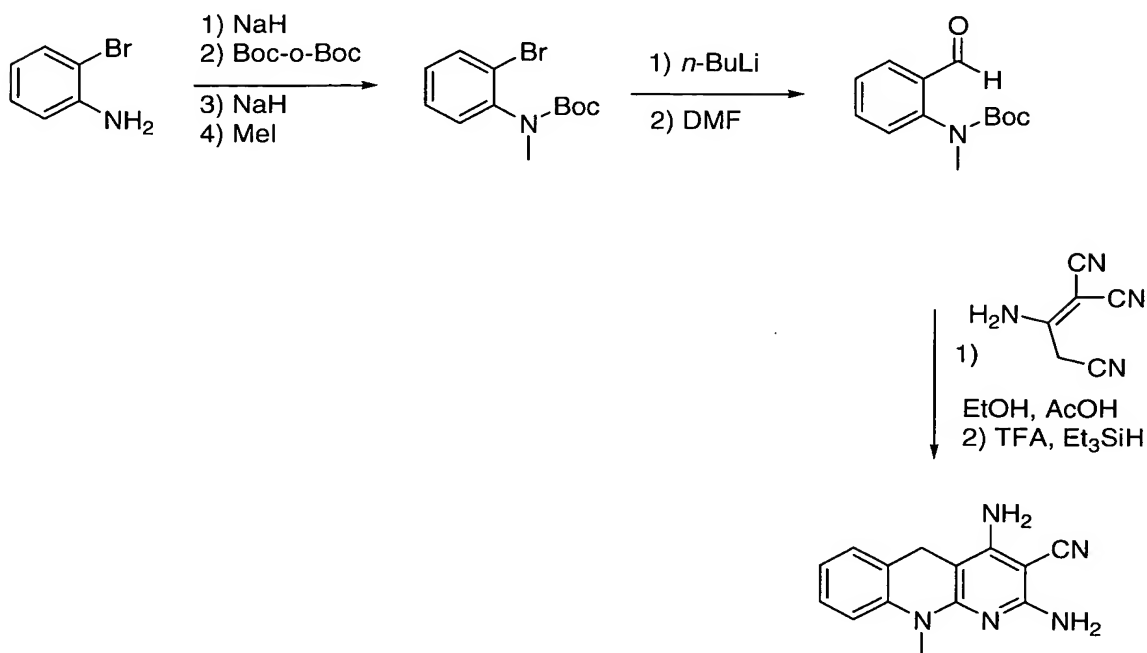
[00083] This illustrates the production of 2-amino-4-(2-furyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.



[00084] 3-(2-furyl)-3-oxopropanenitrile (10 mmol, 1.0 equiv., 1.35g) and malononitrile (10 mmol, 1.0 equiv., 600 $\mu$ L) were combined in pyridine (10mL). The mixture was heated to 100  $^{\circ}$ C for 1 hour. The reaction mixture was diluted with 150 mL dichloromethane and washed with 1 M HCl (3 x 50 mL). The organic layer was dried and evaporated to give a dark oil (GDS-13695-130). The oil was dissolved in EtOH (30 mL) and treated with salicylaldehyde (10 mmol, 1.0 equiv., 1.0 mL) and AcOH (10 mL). The resulting mixture was heated to reflux for 2 hours. The solvents were evaporated and the *in vacuo* and the residue was dissolved in trifluoroacetic acid (15mL). Triethylsilane (10 mL) was added and the solution was stirred overnight. The solvents were evaporated and the residue purified by reverse phase chromatography. The product was isolated as a solid (370mg, 13%). <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta$  7.99 (s, 1H), 7.24-7.20 (m, 2H), 7.08-7.04 (m, 3H), 6.94 (bs, 2H), 6.76 (s, 1H), 3.96 (s, 2H): m/z 290 (M+H).

## EXAMPLE 2

[00085] This illustrates the production of 2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate.



5

[00086] Step 1: (synthesis of *t*-Butyl 2-bromophenyl(methyl)carbamate)

[00087] 2-bromoaniline (25 mmol, 1.0 equiv. 4.3g) was dissolved in THF (150 mL). Sodium hydride (60% in mineral oil, 1.1g) was added and the mixture heated to reflux for 1 hour. After cooling to room temperature, a solution of di-*t*-butyl-dicarbonate in THF (1.0M, 30 mmol, 1.2 equiv., 30 mL) was added followed by sodium hydride (1.1g). The resulting mixture was heated to reflux for 14 hours. After cooling to room temperature, iodomethane (28 mmol, 1.12 equiv., 1.75 mL) was added and the mixture heated to reflux for 3 hours. After cooling to room temperature, the reaction was quenched with water and diluted with ether. The organic layer was washed with sat. aq. NH<sub>4</sub>Cl, sat. aq. NaHCO<sub>3</sub>, and sat. aq. NaCl. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to give a yellow oil. Purification by silica gel chromatography gave the product as a yellow oil (5.9g, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58 (d,

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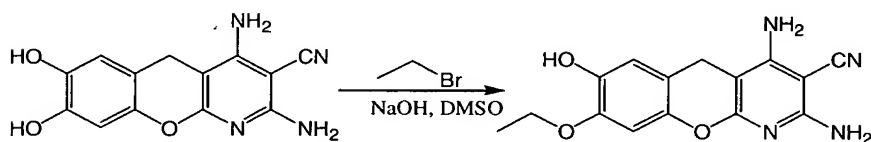
1H), 7.29 (t, 1H), 7.21 (d, 1H), 7.12 (t, 1H), 3.13 (s, 3H), 1.33 (s, 9H): m/z 271 (M+H).

**[00088]** Step 2: (synthesis of 2,4-diamino-10-methyl-5,10-dihydrobenzo[b]-1,8-naphthyridine-3-carbonitrile trifluoroacetate)

5 **[00089]** *t*-Butyl 2-bromophenyl(methyl)carbamate (2.65 mmol, 1.0 equiv., 759 mg) was dissolved in THF (20 mL). The solution was cooled in a dry ice acetone bath and a solution of *n*-BuLi in hexane (1.6M, 1.1 equiv. 1.8 mL) was added dropwise. After 15 minutes, DMF (1 mL) was added and the reaction allowed to warm to room temperature. The reaction  
10 mixture was quenched with sat. aq. NH<sub>4</sub>Cl, and partitioned between ether and water. The organic layer was washed with water and dried over MgSO<sub>4</sub>, filtered and evaporated to get 820 mg of a yellow oil. This oil was carried on immediately without purification or characterization. The resulting oil was treated with 2-amino-1-propene-1,1,3-tricarbonitrile (2  
15 mmol, 265mg), acetic acid (2.0mL), and ethanol (10mL) and the resulting solution was heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (7mL) at 0°C. Triethylsilane (5.0mL) was added via syringe. The reaction stirred for 2 hours before evaporating solvents to get a brown solid. The solid  
20 was washed with dichloromethane and dried to give the product as a light brown solid. (90mg, 9%). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.16 (t, 1H), 7.03 (d, 1H), 6.97-6.91 (m, 2H), 3.70 (s, 2H), 3.34 (s, 3H): m/z 252 (M+H).

### EXAMPLE 3

25 **[00090]** This illustrates the production of 2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.



30 **[00091]** 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (400 mg, 1.0 mmol) and NaOH (166 mg, 4.2 mmol) were



suspended in DMSO (5 mL) and warmed until dissolved. Ethyl bromide was added to the reaction mixture, which was heated to 85°C until disappearance of starting material (HPCL monitoring). After neutralizing with NH<sub>4</sub>Cl, the crude reaction mixture was purified by reverse phase column chromatography (gradient of acetonitrile, H<sub>2</sub>O, 0.05% TFA). Evaporation of the solvent on a lyophilizer gave an orange solid as a TFA salt 2,4-diamino-8-ethoxy-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, which was confirmed by 2D NMR analysis. <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>OD): δ 1.47 (t, 3H), 3.63 (s, 2H), 4.12 (quartet, 2H), 6.59-6.81 (m, 2H). HRMS calcd for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub> (M+H): 299.11. Found: 299.1132.

#### EXAMPLE 4

[00092] This illustrates the production of 2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[00093] 2,4-diamino-8-(2-ethoxyethoxy)-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same method as described above in Example 3, using 2-bromoethyl-ethylether in lieu of 2-bromoethyl-ethylether. <sup>1</sup>H-NMR (300 MHz, CD<sub>3</sub>OD): δ 1.28 (t, 3H), 3.60 (s, 2H), 3.67 (quartet, 2H), 3.86 (s, 2H), 4.19 (s, 2H), 6.58-6.82 (m, 2H). HRMS calcd for C<sub>17</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub> (M+H): 343.13. Found: 343.1418.

#### EXAMPLES 5 - 6

[00094] This illustrates the production of aminocyanopyridine compounds of the present invention.

[00095] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 3. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	HRMS calcd	HRMS found
5	tert-butyl {[2,4-diamino-7-(2-tert-butoxy-2-oxoethoxy)-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl]oxy}acetate trifluoroacetate	499.21	499.2204
6	7,8-bis(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	351.14	351.1445

#### EXAMPLE 7

[00096] This illustrates the production of 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

5 [00097] To a cooled (0 °C) solution of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (1.34mmol, 400mg) and dichloromethane (4.0mL) was slowly added boron tribromide (1M, dichloromethane, 8.04mmol, 8.04mL). The suspension was stirred at 0 °C for 15 minutes, then the ice bath was removed and the reaction warmed to 10 23 °C overnight. After 16h at 23 °C the reaction was cooled to 0°C and carefully neutralized with 2.5N sodium hydroxide to pH = 7. The product was collected by filtration, dissolved in dimethyl sulfoxide (1.0 mL) and purified by reverse phase chromatography. The product was isolated as a pale orange solid (62mg, 17% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 15 9.071(s, 1H), 8.795 (s, 1H), 6.520 (s, 1H), 6.410 (bs, 2H), 6.405(s, 1H), 6.244 (bs, 2H), 3.48 (s, 2H): m/z 271 (M+); HRMS (M+H) calculated for C<sub>13</sub>H<sub>11</sub>N<sub>4</sub>O<sub>3</sub> 271.0753, found 271.0721.

#### EXAMPLE 8

20 [00098] This illustrates the production of 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[00099] 2,4-Dihydroxy-benzaldehyde (43.4mmol, 6.0g), 2-amino-1-propene-1,1,3-tricarbonitrile (43.4mmol, 5.74g), acetic acid (13.0mL), and

ethanol (125.0mL) were combined and heated to reflux for 2 hours. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (160.0mL) at 0°C. Triethylsilane (0.28mol, 32.76g, 45.0mL) was added via syringe. The reaction was stirred for 1 hour at 0°C. 300mL of dichloromethane was added to the reaction and the solid was collected via filtration and washed (2x75mL) with dichloromethane and ether. The product was isolated as a pale orange solid (13.10g, 63% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.958(d, 1H), 6.537 (dd, 1H), 6.390 (d, 1H), 3.510(s, 2H): m/z 255 (M+); HRMS (M+H) calculated for C<sub>13</sub>H<sub>11</sub>N<sub>4</sub>O<sub>2</sub> 255.0804, found 255.0894.

#### EXAMPLE 9

**[000100]** This illustrates the production of 8,10-diamino-2,3-dihydro-11H-[1,4]dioxino[2',3':6,7]chromeno[2,3-b]pyridine-9-carbonitrile.

**[000101]** 2,4-diamino-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.56mmol, 150mg) was dissolved in DMSO (3.0mL) and sodium hydroxide (2.24mmol, 90mg) was added followed by dibromoethane (0.56mmol, 105.20mg, 48.26μL). The dark homogeneous solution was heated to 70°C for 16 hours. The crude reaction mixture was cooled to 23°C, neutralized with trifluoroacetic acid and directly purified via reverse phase chromatography. The product was isolated as a pale orange solid (30mg, 18% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 6.715(s, 1H), 6.553 (s, 1H), 4.215 (bs, 4H), 3.575(s, 2H): m/z 298 (M+H).

#### EXAMPLE 10

**[000102]** This illustrates the production of 2,4-diamino-8-(2-ethoxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

**[000103]** 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.62mmol, 300mg) was dissolved in DMSO (4.0mL) and solid sodium hydroxide (2.79mmol, 111.6mg) was added followed by 2-bromoethyl-ethylether (0.62mmol, 69.9μL). The reaction was heated to 80°C with stirring for 9 hours. The crude reaction was filtered and diluted with DMSO (4.0mL) and purified via reverse phase chromatography. The

product was isolated as a tan solid (80mg, 40% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.180(d, 1H), 6.795 (d, 1H), 6.46 (d, 1H), 4.090 (t, 2H), 3.766(t, 2H), 3.607 (s, 2H), 3.572 (t, 2H), 1.200 (t, 2H); m/z 327 (M+H).

#### EXAMPLE 11

5     **[000104]** This illustrates the production of 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile .

10    **[000105]** 2,4-diamino-8-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10, using 1-(2-chloroethyl)pyridine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (100mg, 46% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.199 (d, 1H), 6.680 (d, 1H), 6.668 (d, 1H), 4.290 (t, 2H), 3.618 (s, 2H), 3.562 (t, 2H), 3.375 (bs, 4H), 2.077(bs, 4H); m/z 352 (M+H). TNFα release assay IC<sub>50</sub>: 2.9μM; Rat LPS Assay 60% inhibition at 20 mpk (IP).

#### EXAMPLE 12

**[000106]** This illustrates the production of 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

20    **[000107]** 2,4-diamino-8-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using 2-bromoethylamine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (167mg, 51% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.180 (bs, 2H), 7.100 (d, 1H), 6.762 (d, 1H), 6.646 (bs, 1H), 4.154 (t, 2H), 3.573 (s, 2H), 3.155 (t, 2H); m/z 398 (M+H). TNFα release assay IC<sub>50</sub>: 6.9μM; Rat LPS Assay 88% inhibition at 20 mpk (IP).

#### EXAMPLE 13

**[000108]** This illustrates the production of [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid.

30    **[000109]** [(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-8-yl)oxy]acetic acid was prepared from 2,4-diamino-8-hydroxy-5H-

chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using bromoacetic acid in lieu of 2-bromoethyl-ethylether.

The product was isolated as a tan solid (110.6mg, 31% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.030 (d, 1H), 6.640 (d, 1H), 6.516 (d, 1H), 6.474 (bs, 2H), 6.278 (bs, 2H), 4.633 (s, 2H), 3.543 (s, 2H); m/z 427 (M+H).

#### EXAMPLE 14

**[000110]** This illustrates the production of 2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

**[000111]** 2,4-diamino-8-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using 2-bromoethanol in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (120mg, 35% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.025 (d, 1H), 6.670 (d, 1H), 6.550 (d, 1H), 3.931 (t, 2H), 3.662 (t, 2H), 3.546 (s, 2H); m/z 413 (M+H).

#### EXAMPLE 15

**[000112]** This illustrates the production of 2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

**[000113]** 2,4-diamino-8-(2-morpholin-4-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared from 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile in the same manner as described in Example 10 using 1-(2-chloroethyl)morpholine in lieu of 2-bromoethyl-ethylether. The product was isolated as a tan solid (80mg, 17% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.071 (d, 1H), 6.714 (d, 1H), 6.654 (d, 1H), 6.527 (bs, 2H), 6.323 (bs, 2H), 4.311 (t, 2H), 3.938 (m, 2H), 3.664 (t, 2H), 3.558 (s, 2H), 3.534 (m, 2H), 3.451 (m, 2H), 3.158 (m, 2H); m/z 482 (M+H).

#### EXAMPLES 16 - 22

**[000114]** This illustrates the production of aminocyanopyridine compounds of the present invention.

**[000115]** The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 10.

NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	m/z (M+H)
16	2,4-diamino-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	269
17	7,9-diamino-10H-[1,3]dioxolo[6,7]chromeno[2,3-b]pyridine-8-carbonitrile	283
18	8-(allyloxy)-2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	295
19	2-amino-8-ethoxy-4-(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	311
20	8-ethoxy-2,4-bis(ethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	339
21	2-amino-8-(2-ethoxyethoxy)-4-[(2-ethoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	399
22	2,4-diamino-8-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	326

5

### EXAMPLE 23

[000116] This illustrates the production of 2,4-diamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate).

[000117] 3-Methoxysalicylaldehyde (10 mmol, 1.52 g), 2-amino-1-propene-1,1,3-tricarbonitrile (10 mmol, 1.32 g) acetic acid (2.5 mL), and ethanol (40 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (15 mL) at 0°C. Triethylsilane (62 mmol, 7.2 g, 10 mL) was added via syringe. The reaction stirred for one hour at room temperature. Dichloromethane (100 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a white solid (2.5 g, 50% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 7.08 (t, *J* = 8Hz, 1H), 7.00-6.80 (m, 2H), 6.73 (d, *J* = 7.4 Hz, 2H), 3.83(s, 3H), 3.68 (s, 2H); m/z 269

(M+H); Anal. calculated for  $C_{14}H_{12}N_4O_2 \cdot 2CF_3CO_2H$ : C, 43.56; H, 2.84; N, 11.29, found: C, 43.40; H, 2.98; N, 11.32.

#### EXAMPLE 24

5 **[000118]** This illustrates the production of 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

**[000119]** 2,4-diamino-7-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 23, except that 5-hydroxysalicylaldehyde was used in place of methoxysalicylaldehyde. The product was isolated as a pink solid (951 mg, 30% yield).  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  6.88 (d,  $J$  = 8.8 Hz, 1H), 6.63 (d,  $J$ =8.7 Hz, 1H), 6.55(s, 1H), 3.6 (s, 2H):  $m/z$  255 (M+H); Anal. calculated for  $C_{13}H_{10}N_4O_2 \cdot 1.5CF_3CO_2H \cdot 0.5H_2O$ : C, 44.25; H, 2.90; N, 12.90, found: C, 44.04; H, 3.05; N, 12.84.

#### EXAMPLE 25

15 **[000120]** This illustrates the production of 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile Bis(trifluoroacetate).

**[000121]** 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 23 except that salicylaldehyde was used in place of methoxysalicylaldehyde. The product was isolated as a light tan solid (1.26 g, 33% yield).  $^1H$  NMR (300 MHz, DMSO- $d_6$ ),  $\delta$  7.30-6.90 (m, 6H), 3.7 (s, 2H);  $m/z$  239 (M+H); Anal. Calcd for  $C_{13}H_{10}N_4O \cdot 2CF_3CO_2H \cdot 0.25H_2O$ : C, 43.37; H, 2.68; N, 11.90, found: C, 43.07; H, 2.81; N, 11.79.

#### EXAMPLE 26

25 **[000122]** This illustrates the production of 2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

**[000123]** 2,4-diamino-8,9-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 23, except that 2,3,4-trihydroxybenzaldehyde was used in place of methoxysalicylaldehyde. The product was isolated as a white solid (3.6 g, 82% yield).  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  7.1 (bs, 3H), 6.58 (d,  $J$  = 8 Hz, 1H), 6.47 (d,  $J$  = 8 Hz, 1H), 3.75 (s, 2H);  $m/z$  271(M+H).

#### EXAMPLE 27

[000124] This illustrates the production of 2,4-diamino-9-hydroxy-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

5 [000125] 2,3-dihydroxy-4-methoxybenzaldehyde (3 mmol, 506 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3 mmol, 398 mg), acetic acid (1 mL), and ethanol (15 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10 mL) at 0°C. Triethylsilane (25 mmol, 2.88 g, 4 mL) was added via syringe. The reaction stirred for overnight at room  
10 temperature to give a yellow slurry. Dichloromethane (50 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a yellow solid (482 mg, 35% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 6.73 (d, *J*=8.5 Hz, 1H), 6.57 (d, *J*=8.5 Hz, 1H), 3.77(s, 3H), 3.57 (s, 2H); *m/z* 285 (M+H); Anal.  
15 calculated for C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>-1.25CF<sub>3</sub>CO<sub>2</sub>H -1.5H<sub>2</sub>O: C, 43.58; H, 3.62; N, 12.32, found: C, 43.80; H, 3.22; N, 12.65.

#### EXAMPLE 28

[000126] This illustrates the production of 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

20 [000127] 2,3-dihydroxybenzaldehyde (5 mmol, 691 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (5 mmol, 661 mg), acetic acid (1.2 mL), and ethanol (20 mL) were combined and heated to reflux overnight. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (20 mL) at 0°C. Triethylsilane (62 mmol, 7.2 g, 10 mL)  
25 was added via syringe. The reaction stirred for two and one-half days at room temperature to give a solution, which was concentrated *in vacuo*. The residue was stirred in methanol and the slurry was filtered. The product was obtained as a brown solid by concentrating the filtrate (167 mg, 9% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 6.91 (t, *J* = 7.7 Hz, 1H),  
30 6.86-6.70 (m, 2H), 6.59 (d, *J* = 7.3 Hz 1H), 3.61 (s, 2H); *m/z* 255 (M+H).



#### EXAMPLE 29

[000128] This illustrates the production of 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000129] Step 1: Preparation of 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile: 5-nitrosalicylaldehyde (132 mmol, 22.00 g), 2-amino-1-propene-1,1,3-tricarbonitrile (132 mmol, 17.39 g), acetic acid (31 mL), and ethanol (500 mL) were combined and heated to reflux overnight. The resulting slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (350 mL) at 0°C. Triethylsilane (1.40 mol, 162 g, 225 mL) was added. The mixture was heated overnight at 66 °C. The mixture was cooled and concentrated *in vacuo*. Triturating with methanol gave 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile as a yellow solid (22.48 g, 60% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 8.13 (d, *J* = 9.0 Hz, 1H), 8.00 (s, 1H), 7.25 (d, *J* = 9.0 Hz, 1H), 6.70 (br s, 2H), 6.50 (bs, 2H), 3.82 (s, 2H); *m/z* 284 (M+H); Anal. Calcd for C<sub>13</sub>H<sub>9</sub>N<sub>5</sub>O<sub>3</sub>·0.5H<sub>2</sub>O: C, 53.43; H, 3.45; N, 23.96, found: C, 53.41; H, 3.17; N, 23.71.

[000130] Step 2: A mixture of 2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described above, (0.55 mmol, 155 mg) and Pd/C (35 mg, 10% on activated carbon) in DMF (15 mL) was stirred under an atmosphere of hydrogen (balloon) for 3.5 hours. The catalyst was removed by filtration using a plug of celite. The filtrate was concentrated *in vacuo* and the residue was triturated with methanol to give 2,4,7-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile as a grey solid (109 mg, 79% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 6.72 (d, *J* = 8.0 Hz, 1H), 6.39-6.5(m, 4H), 6.25 (s, 2H), 3.52 (s, 2H); *m/z* 254 (M+H).

#### EXAMPLE 30

[000131] This illustrates the production of 2,4-diamino-9-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000132] 3-Fluoro-2-hydroxybenzaldehyde (3.45 mmol, 484 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3.50 mmol, 463 mg), acetic acid (0.9 mL) and ethanol (27 mL) were combined and heated to reflux for 14 hours. The reaction slurry was concentrated *in vacuo* and then dissolved in

trifluoroacetic acid (10.5 mL). Triethylsilane (43mmol, 4.97 g, 6.9 mL) was added via syringe. The reaction was heated to reflux for 5 hours.

Dichloromethane (50 mL) was added to the reaction and the solid formed was collected via filtration and washed with methanol. The product was isolated as a white solid (377 mg, 30% yield). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ 7.25-7.19 (m, 1H), 7.15-7.08 (m, 1H), 7.00-6.96 (m, 1H), 6.70 (bs, 2H), 6.51 (bs, 2H), 3.75 (s, 2H); m/z 257 (M+H).

#### EXAMPLE 31

[000133] This illustrates the production of 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-7-carboxylic acid Bis(trifluoroacetate).

[000134] 5-Carboxysalicylaldehyde (3 mmol, 500 mg), 2-amino-1-propene-1,1,3-tricarbonitrile (3 mmol, 396 mg) acetic acid (1.2 mL), and ethanol (15 mL) were combined and heated to reflux for 2.5 days. The reaction slurry was concentrated *in vacuo* and then dissolved in trifluoroacetic acid (10 mL). Triethylsilane (62 mmol, 7.2g, 10 mL) was added via syringe. The reaction was stirred for 4 hours at 50 °C and then was stirred overnight at room temperature. Dichloromethane (20 mL) was added to the reaction and the solid formed was collected via filtration and washed with dichloromethane (2x). The product was isolated as a yellow solid (560 mg, 36% yield). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.85 (s, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.80 (br s, 2H), 3.85 (s, 2H); m/z 283 (M+H); anal. Calculated for C<sub>14</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub>·2CF<sub>3</sub>CO<sub>2</sub>H·0.25H<sub>2</sub>O: C, 42.00; H, 2.45; N, 10.88, found: C, 42.30; H, 2.31; N, 10.51.

#### EXAMPLE 32

[000135] This illustrates the production of 2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

[000136] 2,4-diamino-6,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 31, except that 2,4,6-trihydroxybenzaldehyde was used in place of 5-carboxysalicylaldehyde. The product was isolated as an orange solid (106 mg, 9% yield). <sup>1</sup>H NMR (free base, 300 MHz, DMSO-d<sub>6</sub>): δ 9.65 (s, 1H),

9.40 (s, 1H), 6.41 (s, 2H), 6.35 (s, 2H), 6.10 (s, 1H), 5.85 (s, 1H), 3.31 (s, 2H); m/z 271 (M+H).

EXAMPLES 33 - 51

5 [000137] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000138] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 29. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

10

Ex. No.	Compound name	M+H
33	2,4-diamino-7-(dimethylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	282
34	2,4-diamino-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	284
35	2,4-diamino-7-chloro-9-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	287
36	2,4-diamino-6,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	299
37	2,4-diamino-7-(trifluoromethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	323
38	2,4-diamino-7-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	347
39	2,4-diamino-9-methoxy-7-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	314
40	2,4-diamino-8-methyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	253
41	2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylic acid bis(trifluoroacetate)	283
42	2,4-diamino-6-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile bis(trifluoroacetate)	269

Ex. No.	Compound nam	M+H
43	2,4-diamino-9-bromo-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	351
44	2,4-diamino-6-bromo-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	347
45	2,4,7-triamino-9-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	284
46	2,4-diamino-9-nitro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	284
47	2,4,9-triamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	254
48	2,4-diamino-7-fluoro-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	257
49	2,4-diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile	273
50	2,4-diamino-9-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile	295
51	ethyl 2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridine-9-carboxylate	311

#### EXAMPLE 52

[000139] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

5 [000140] Step 1: Production of 5-Nitrothiosalicylaldehyde: A mixture of 2-chloro-5-nitrobenzaldehyde (2g, 11 mmol) and lithium sulfide (0.54 g, 11.7 mmol) in 30 mL of anhydrous DMSO was stirred under nitrogen at room temperature overnight. The solution was then added to a mixture of ice-water, acidified with 2N HCl and extracted with ether three times. The  
10 combined ether layers were washed with water, brine, dried, filtered and concentrated to give the crude 5-nitro-2-thiosalicylaldehyde as an orange solid (1.3g, 65% yield)

**[000141]** Step 2: A solution of the crude 5-nitro-2-thiosalicylaldehyde (1.3g, 7.1 mmol), 2-amino-1-propene-1,1,3-tricarbonitrile (7.6 mmol, 1 g), acetic acid (2.5 mL) in 70 mL of ethanol was heated at 76°C under nitrogen overnight. The reaction mixture was cooled to room temperature and filtered. The solid was washed with ethanol to give the desired tricyclic intermediate as a light brown solid (1.5g, 71.4% yield).

**[000142]** Step 3: A reaction mixture of the aforementioned tricyclic intermediate (1.2 g, 4 mmol) and triethylsilane (15 mL) in 100 mL of trifluoroacetic acid was heated at between 60-65°C under nitrogen for 2 hours. After that, the solution was cooled to room temperature and concentrated in vacuo. Ether was added to the residue. The solid was filtered, washed with additional ether to give 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile as an orange powder (0.9 g, 75% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN + D<sub>2</sub>O) δ 8.089 (d, 1H), 8.046 (dd, 1H), 7.609 (d, 1H), 3.898 (s, 2H); m/z 300 (M+H).

#### EXAMPLE 53

**[000143]** This illustrates the production of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate.

**[000144]** To 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (produced as described above in Example 52; 0.8 g, 2.7 mmol) in 9 mL of 50% (by weight) of ethanol-water was added iron powder (0.55 g, 10 mmol). The mixture was heated to 60°C and then 0.5 mL of HCl/ethanol (prepared from 5.2 mL of conc. HCl and 25 mL of 50% of ethanol-water) was added. The resulting mixture was heated at 76°C for 2.5 hours and filtered hot. The solid was washed with 50% ethanol-water. The filtrates were combined and concentrated *in vacuo* to give a brownish yellow solid. The solid was then dissolved in acetonitrile, filtered to remove a small amount of insoluble solid and concentrated *in vacuo*. The resulting solid was then washed with methanol and trifluoroacetic acid. The trifluoroacetic acid filtrate was concentrated in vacuo to give an amber oil. Ether was added and the solid was filtered, washed with ether, air-dried overnight and then dried in a vacuum oven at 44°C for 2 hours to

give the product as a grayish solid (0.53 g, 71% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN} + \text{D}_2\text{O}$ )  $\delta$  7.153 (d, 1H), 6.792 (s, 1H), 6.698 (d, 1H), 3.628 (s, 2H);  $m/z$  270 (M+H).

#### EXAMPLE 54

5 [000145] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000146] To a solution of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Example 52, (3 g, 10 mmol) in 125 mL of trifluoroacetic acid cooled with a water bath was added dropwise 30% hydrogen peroxide (8 g). After addition was completed, the water bath was removed. After 4 hours, additional 30% hydrogen peroxide (2 g) was added and stirring at room temperature was continued for additional 2 hours. After that, water (20 mL) was added and the resulting solution was concentrated to about 70 mL. Then more water was added and the yellow suspension was stirred at room temperature overnight. The suspension was filtered and washed with water to give the desired product as a yellow solid (2 g, 60.4% yield).  $^1\text{H}$  NMR(400MHz, DMSO +  $\text{D}_2\text{O}$ )  $\delta$  8.350 (dd, 1H), 8.265 (d, 1H), 8.220 (d, 1H), 4.160 (s, 2H);  $m/z$  332 (M+H).

#### EXAMPLE 55

20 [000147] This illustrates the production of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000148] A mixture of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, produced as described in Example 54, (0.8 g, 2.4 mmol) and iron powder (0.58 g, 10 mmol) in 50% of ethanol-water (10 mL) was heated to 70 $^{\circ}\text{C}$ , then 1 mL of HCl/ethanol (prepared from 5.2 mL of conc. HCl and 25 mL of 50% of ethanol-water) was added. The resulting mixture was heated at 76 $^{\circ}\text{C}$  for 3 hours and filtered hot. The solid was washed with methanol and trifluoroacetic acid. The trifluoroacetic acid filtrate was concentrated *in vacuo* and ether was added to the viscous oil. The solid was filtered and washed with ether to give the desired product as a beige solid (0.42 g, 57.5% yield).  $^1\text{H}$  NMR

(400 MHz, DMSO + D<sub>2</sub>O)  $\delta$  7.521 (d, 1H), 6.60 (dd, 1H), 6.529 (s, 1H), 3.753 (s, 2H); m/z 302 (M+H).

#### EXAMPLE 56

5 [000149] This illustrates the production of 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

[000150] 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared as a bis-trifluoroacetate in the same manner as described in Example 52, except that 2,5-difluorobenzaldehyde was used as the starting material in place of 2-chloro-5-nitrobenzaldehyde. The  
10 product was isolated as a beige solid (0.35 g, 35% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN + D<sub>2</sub>O),  $\delta$  7.425 (dd, 1H), 7.153 (dd, 1 H), 7.088 (dt, 1H) 3.743 (s, 2H); m/z 273 (M+H)

#### EXAMPLE 57

15 [000151] This illustrates the production of 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile Bis(trifluoroacetate).

[000152] 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 52, except that 2-fluorobenzaldehyde was used as the starting material in place of 2-chloro-5-nitrobenzaldehyde. The product was isolated as a beige solid (1.8 g,  
20 47.4% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN + D<sub>2</sub>O)  $\delta$  7.271-7.435 (m, 4H), 3.785 (s, 2 H); m/z 255 (M+H).

#### EXAMPLE 58

[000153] This illustrates the production of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

25 [000154] 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile was prepared in the same manner as described in Example 52, except that 2-fluoro-5-methoxybenzaldehyde was used as the starting material. The product was isolated as a beige solid (0.5 g, 49% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>CN + D<sub>2</sub>O)  $\delta$  7.329 (d, 1H), 6.938 (d, 1H), 6.885 (dd, 1H), 3.795 (s, 3H), 3.710 (s, 2H); m/z 285 (M+H)  
30

EXAMPLE 59

[000155] This illustrates the production of 2,4-diamino-7-hydroxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile.

5 [000156] A mixture of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (0.3 g, 0.59 mmol), produced as described in Example 58, and 0.6 mL of boron tribromide (6.4 mmol) in 30 mL of methylene chloride was stirred at room temperature for 18 h. After that, the solid was filtered, washed with methylene chloride, water and methanol. The methanol filtrate was concentrated to give a solid, which  
10 was washed with water, acetonitrile and ether to give the desired product as a red solid (54 mg, 33.6% yield). <sup>1</sup>H NMR (400 MHz, DMSO + D<sub>2</sub>O) δ 9.520 (s, 1H), 8.111 (d, 1H), 7.561 (d, 1H), 7.522 (s, 2H); m/z 271 (M+H).

EXAMPLE 60

15 [000157] This illustrates the production of 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide (an alternative procedure).

[000158] A mixture of 2,4,7-triamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile (0.1 g, 0.26 mmol), produced as described in Example 55, and 30% hydrogen peroxide (1.5 mL) in 3 mL of trifluoroacetic acid was stirred  
20 at room temperature overnight. Water (30 mL) was then added and the resulting suspension was stirred at ambient temperature for 2 hours. The solid was filtered to give the desired product as a yellow solid (18 mg, 8.6% yield): <sup>1</sup>H NMR (400 MHz, DMSO + D<sub>2</sub>O) δ 8.353 (dd, 1H), 8.263 (d, 1H), 8.228 (d, 1H), 4.163 (s, 2H); m/z 332 (M+H).

25 EXAMPLE 61

[000159] This illustrates the production of 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000160] 2,4-diamino-7-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 60. The product was isolated as a yellow  
30 solid (51 mg, 32.7% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.028 (q, 1H),



7.433 (dt, 1H), 7.253 (d, 1H), 7.162 (bs, 1H), 6.917 (bs, 1H), 4.024 (s, 2H);  
m/z 305 (M+H).

#### EXAMPLE 62

5 [000161] This illustrates the production of 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000162] 2,4-diamino-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 60. The product was isolated as a yellow solid (73 mg, 42.9%  
10 yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.945 (dd, 1H), 7.762 (dt, 1H), 7.568 (t, 1H), 7.467 (d, 2H), 7.179 (bs, 2H), 6.886 (bs, 1H), 4.009 (s, 2H); m/z 287 (M+H).

#### EXAMPLE 63

15 [000163] This illustrates the production of 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide.

[000164] 2,4-diamino-7-methoxy-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide was prepared in the same manner as 2,4-diamino-7-nitro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide, as described in Example 60. The product was isolated as a light  
20 brown solid (110 mg, 34.2% yield). <sup>1</sup>H NMR (400 MHz, DMSO + D<sub>2</sub>O) δ 7.858 (d, 1H), 7.107 (dd, 1H), 6.972 (d, 1H), 3.942 (2, 2H), 3.833 (s, 3H); m/z 316 (M+H).

#### EXAMPLES 64 - 65

25 [000165] This illustrates the production of aminocyanopyridine compounds of the present invention.

[000166] The aminocyanopyridine compounds shown in the table below were prepared according to the general method described in Example 60. NMR analysis was carried out according to the method described above, and resulting data for each of the compounds is provided in the table.

Ex. No.	Compound name	m/z (M+H)
64	2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	273
65	2,4-diamino-9-fluoro-5H-thiochromeno[2,3-b]pyridine-3-carbonitrile 10,10-dioxide	305

#### EXAMPLES 66 - 81

5 [000167] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

##### General procedure for the N-alkylation:

10 [000168] To a solution of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (1.34 mmol) and the corresponding halide (2.01 mmol) in dimethylformamide ( 5 mL) is added sodium hydride (80 mg, 2.01 mmol). The reaction mixture is stirred at room temperature or heated to 40°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by reverse phase chromatography. Both the mono alkylated and dialkylated product were isolated.

15 [000169] The following compounds were prepared using the procedure described above:

Example 66: 2-amino-4-[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

20 Example 67: 2,4-bis[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 68: 2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 69: 2-amino-4-[[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

25 Example 70: 2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 71: 7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 72: 2,4-bis(glyciny)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate,

5 Example 73: *N*-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine,

Example 74: 7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

10 Example 75: 2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 76: 2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile

Example 77: 2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

15 Example 78: 7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 79: 2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

20 Example 80: 2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 81: 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

**[000170]** General procedure for the demethylation:

25 **[000171]** To a solution of the corresponding dimethoxy aryl analog (0.68 mmol) in dichloromethane (2mL) is slowly added boron tribromide (1M, dichloromethane, 3.38mmol, 3.38mL). The reaction mixture is stirred at room temperature for 4 hours, quenched with 5% aqueous sodium hydroxide, then neutralized with 5% aqueous HCl. The resulting solid is collected and the aqueous layer is extracted with dichloromethane. The  
30 organic layer is concentrated under vacuum and combined with the solid. The residue is purified by reverse phase chromatography.

EXAMPLE 82

[000172] This illustrates the production of 2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000173] 2-amino-4-(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared using the demethylation procedure described above starting with 2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile. <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.65(q, 2H), 2.5 (s, 2H), 1.25 (t, 3H); m/z 299.15 (M+H); HRMS (M+H) calculated for C<sub>15</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub> 299.1139, found 299.1113.

EXAMPLE 83

[000174] This illustrates the production of 2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000175] 2-amino-7,8-dihydroxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile is prepared using the demethylation procedure described above for Examples 66 - 81 starting with 2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile. <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.55(m, 2H), 2.5 (s, 2H), 1.6(m, 2H), 1.35 (t, 3H); m/z 313.16 (M+H); HRMS (M+H) calculated for C<sub>16</sub>H<sub>17</sub>N<sub>4</sub>O<sub>3</sub> 313.1295, found 313.1325.

EXAMPLE 84

[000176] This illustrates the production of 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

[000177] 2-amino-7,8-dihydroxy-4-[(2-hydroxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared using the demethylation procedure described above for Examples 66 - 81, starting with 2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile. <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.5(s, 1H), 6.4 (s, 1H), 3.65(m, 2H), 3.55(m, 2H), 2.5 (s, 2H); m/z 315.13 (M+H).

EXAMPLE 85

[000178] This illustrates the production of 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

5 [000179] 2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile was prepared by using the procedure described in Examples 66 - 81.

EXAMPLES 86 - 91

[000180] This illustrates the production of certain aminocyanopyridine compounds of the present invention.

10 General procedure for the O-alkylation of phenol 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile:

[000181] A solution of 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (0.73 mmol), and powdered sodium hydroxide (117 mg, 2.93 mmol)) in dimethyl sulfoxide (4 mL) is heated to 50°C for  
15 five minutes. The corresponding halide is added and the reaction mixture is stirred at 50°C or 75°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by purified by reverse phase chromatography.

[000182] The following compounds were prepared using the above  
20 procedure:

Example 86: 2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 87: (2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid,

25 Example 88: 2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

Example 89: 2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile,

30 Example 90: 2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

Example 91: 2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

EXAMPLES 92 - 120

**[000183]** This illustrates the production of certain aminocyanopyridine compounds of the present invention.

**[000184]** General procedure for the Mannich condensation:

5 **[000185]** To a solution of the corresponding phenol (0.92 mmol) in ethanol (5 mL) is added formic acid (37% solution, 76  $\mu$ L, 1.01 mmol) and piperidine (100  $\mu$ L, 1.01 mmol). The reaction mixture is stirred at 75°C until completion. The mixture is quenched with saturated aqueous ammonium chloride and directly purified by reverse phase chromatography and each regioisomer isolated.

10 **[000186]** The following compounds were prepared using the above procedure:

Example 92: 2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, and

15 Example 93: 2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, were produced starting with 2,4-diamino-9-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Examples 66 - 81, and

20 Example 94: 2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile, was produced starting with 2,4-diamino-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile, produced as described in Example 8.

25 **[000187]** Other aminocyanopyridine compounds of the present invention can be produced by the same general method, and are shown in the table below along with NMR parameters, which were determined as described above.

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
95	2,4-diamino-9-hydroxy-8-(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	352.26	352.1768	352.1778	C <sub>19</sub> H <sub>21</sub> N <sub>5</sub> O <sub>2</sub>
96	2,4-diamino-8-hydroxy-7,9-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	449.33	449.266	449.2637	C <sub>25</sub> H <sub>32</sub> N <sub>6</sub> O <sub>2</sub>
97	2,4-diamino-9-hydroxy-6,8-bis(piperidin-1-ylmethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	449.32	449.266	449.2629	C <sub>25</sub> H <sub>32</sub> N <sub>6</sub> O <sub>2</sub>
98	2,4-diamino-9-(2-pyrrolidin-1-ylethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	352.26	352.1768	352.1777	C <sub>19</sub> H <sub>21</sub> N <sub>5</sub> O <sub>2</sub>
99	2,4-diamino-9-(pyridin-4-ylmethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	346.16	346.1299	346.1344	C <sub>19</sub> H <sub>15</sub> N <sub>5</sub> O <sub>2</sub>
100	2,4-diamino-9-[2-(dimethylamino)ethoxy]-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	326.24	326.1612	326.1607	C <sub>17</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub>
101	2,4-diamino-9-(2-hydroxyethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	299.19	299.1139	299.1153	C <sub>15</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub>
102	[(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-9-yl)oxy]acetic acid trifluoroacetate	313.14	313.0931	313.0972	C <sub>15</sub> H <sub>12</sub> N <sub>4</sub> O <sub>4</sub>
103	2,4-diamino-9-(2-aminoethoxy)-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	298.18	298.1299	298.1303	C <sub>15</sub> H <sub>15</sub> N <sub>5</sub> O <sub>2</sub>

Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
104	2,4-bis(ethylamino)-7,8-dihydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	327.2	327.1452	327.1493	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub>
105	2-amino-4-[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	370.27	370.1874	370.1869	C <sub>19</sub> H <sub>23</sub> N <sub>5</sub> O <sub>3</sub>
106	2,4-bis[[2-(dimethylamino)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	441.31	441.2609	411.2629	C <sub>23</sub> H <sub>32</sub> N <sub>6</sub> O <sub>3</sub>
107	2-amino-4-[(2-aminoethyl)amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	342.22	342.1561	342.1546	C <sub>17</sub> H <sub>19</sub> N <sub>5</sub> O <sub>3</sub>
108	2-amino-4-[[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]amino]-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	472.21			C <sub>25</sub> H <sub>21</sub> N <sub>5</sub> O <sub>5</sub>
109	2-amino-7,8-dimethoxy-4-[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	396.32	396.203	396.2061	C <sub>21</sub> H <sub>25</sub> N <sub>5</sub> O <sub>3</sub>
110	7,8-dimethoxy-2,4-bis[(2-pyrrolidin-1-ylethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	493.44			C <sub>27</sub> H <sub>36</sub> N <sub>6</sub> O <sub>3</sub>
111	2,4-bis(glycinyl)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile trifluoroacetate	415.33			C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O <sub>7</sub>
112	N-(2-amino-3-cyano-7,8-dimethoxy-5H-chromeno[2,3-b]pyridin-4-yl)glycine	357.26	357.1193	357.1818	C <sub>17</sub> H <sub>16</sub> N <sub>4</sub> O <sub>5</sub>



Ex. No.	Compound name	m/z (M+H)	HRMS Theor.	HRMS Found	Formula Calcd for
113	7,8-dimethoxy-2,4-bis[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	415.3	415.1976	415.1972	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>5</sub>
114	2-amino-7,8-dimethoxy-4-[(2-methoxyethyl)amino]-5H-chromeno[2,3-b]pyridine-3-carbonitrile	357.25	357.1557	357.2538	C <sub>18</sub> H <sub>20</sub> N <sub>4</sub> O <sub>4</sub>
115	2,4-bis(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	411.35	411.2391	411.2391	C <sub>23</sub> H <sub>30</sub> N <sub>4</sub> O <sub>3</sub>
116	2-amino-4-(butylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	355.26	355.1765	355.1763	C <sub>19</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub>
117	7,8-dimethoxy-2,4-bis(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	383.31	383.2078	383.2085	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>3</sub>
118	2-amino-7,8-dimethoxy-4-(propylamino)-5H-chromeno[2,3-b]pyridine-3-carbonitrile	341.25	341.1608	341.1623	C <sub>18</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub>
119	2,4-bis(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	355.27	355.1765	355.1784	C <sub>19</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub>
120	2-amino-4-(ethylamino)-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	327.21	327.1452	327.142	C <sub>17</sub> H <sub>18</sub> N <sub>4</sub> O <sub>3</sub>

#### EXAMPLE 121

**[000188]** This illustrates the production of 2,4-diamino-7,8-dimethoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile.

- 5 **[000189]** To a stirred solution of 3,4-dimethoxyphenol (35.7mmol, 5.5g) and piperidine (40mmol, 3.4g) in ethanol (50mL) was slowly added formaldehyde (37%, water, 39.5mmol, 3.2g). The mixture was stirred at room temperature for 4 hours and then evaporated *in vacuo* and the

resultant residue was partitioned between ethyl acetate (100mL) and water (100 mL). The organic layer was washed with water, dried (MgSO<sub>4</sub>) and evaporated to give a colorless oily residue. To a solution of the above oily product in acetone was added methyl iodide (100mmol, 14.2g) and the mixture was stirred at room temperature overnight. The resultant white precipitate was collected by filtration, washed with ether and air-dried to give 8.14 g of a white solid.

**[000190]** To a slurry of the above solid (1mmol, 390mg) and 2-amino-1-propene-1,1,3-tricarbonitrile (1mmol, 132mg) in ethanol (10mL) was added triethylamine (0.5mL) and the resultant solution was heated at reflux for 30 minutes. After cooling to room temperature, the precipitate was collected by filtration, washed with ethanol and air-dried to give the product as a white solid (178mg, 60% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 6.582 (s, 1H), 6.574 (s, 1H), 6.406 (s, 2H), 6.241 (s, 2H), 3.686 (s, 3H), 3.671 (s, 3H), 3.524 (s, 2H); m/z 299 (M+H).

#### EXAMPLE 122

**[000191]** This illustrates the production of 2(2,4-diamino-3-cyano-8-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

**[000192]** To a solution of 2-hydroxy-4-methoxybenzaldehyde (10mmol, 1.52g) and malononitrile (40mmol, 2.64g) in ethanol (250mL) was added six drops of piperidine. The mixture was heated at 50°C for 10 minutes and then stirred at room temperature for 5 hours. The resultant precipitate was collected by filtration and recrystallized from methanol to give the product as a pale yellow solid (1.19g, 36% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.274(d, 1H), 6.999 (s, 2H), 6.817 (dd, 1H), 6.733 (d, 1H), 6.619 (s, 2H), 4.804 (d, 1H), 4.734 (d, 1H), 3.757 (s, 3H); m/z 333 (M+H).

#### EXAMPLE 123

**[000193]** This illustrates the production of 2(2,4-diamino-3-cyano-7-bromo-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

**[000194]** To a solution of 5-bromo-2-hydroxybenzaldehyde (10mmol, 2g) and malononitrile (35mmol, 2.31g) in ethanol (200mL) was added six drops of piperidine and the mixture was stirred at room temperature for 30

hours. The resultant precipitate was collected by filtration and recrystallized from methanol to give the product as a white solid (1.68g, 44% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.489 (dd, 1H), 7.344 (d, 1H), 7.230 (d, 1H), 7.063 (s, 2H), 6.686 (s, 2H), 4.876 (d, 1H), 4.850 (d, 1H); m/z 381, 383 (M+H).

#### EXAMPLE 124

**[000195]** This illustrates the production of 2(2,4-diamino-3-cyano-7-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

**[000196]** To a solution of 2-hydroxy-5-methoxybenzaldehyde (10mmol, 1.52g) and malononitrile (40mmol, 2.64g) in ethanol (350mL) was added six drops of piperidine and the mixture was stirred at room temperature for 18 hours. The resultant precipitate was collected by filtration, successively washed with ethanol and ether and and air-dried to give the product as a grey solid (1.42g, 43% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.107(d, 1H), 6.990 (m, 3H), 6.865 (d, 1H), 6.603 (s, 2H), 4.850 (d, 1H), 4.794 (d, 1H), 3.724 (s, 3H); m/z 333 (M+H).

#### EXAMPLE 125

**[000197]** This illustrates the production of 2(2,4-diamino-3-cyano-8-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile.

**[000198]** To a solution of 2,4-dihydroxybenzaldehyde (10mmol, 1.38g) and malononitrile (40mmol, 2.64g) in ethanol (350mL) was added six drops of piperidine and the mixture was stirred at room temperature for 5 hours. The resultant precipitate was collected by filtration, washed successively with ethanol and ether and air-dried to give the product as a yellow solid (1.62g, 51% yield). <sup>1</sup>H NMR (400 MHz, DMSO) δ 9.887 (s, 1H), 7.162 (d, 1H), 6.971 (s, 2H), 6.613 (dd, 1H), 6.597 (s, 2H), 6.497 (d, 1H), 4.743 (d, 1H), 4.687 (d, 1H); m/z 319 (M+H).

#### EXAMPLE 126 - 135

**[000199]** This illustrates the production of certain aminocyanopyridine compounds of the present invention.

**[000200]** The aminocyanopyridine compounds listed in the table below were produced according to the general method described in Example

123. NMR analysis was carried out for each material according to the method described above. The names and NMR data for each compound is provided in the table.

Ex. No.	Compound name	m/z (M+H)
126	2,4-diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	269
127	2(2,4-diamino-3-cyano-7-hydroxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	319
128	2,4-diamino-7-bromo-5H-chromeno[2,3-b]pyridine-3-carbonitrile	317, 319
129	2(2,4-diamino-3-cyano-9-methoxy-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	333
130	2,4-diamino-5-(2-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	363
131	2(2,4-diamino-3-cyano-7-chloro-5H-chromeno[2,3-b]pyridin-5-yl)malononitrile	337
132	2,4-diamino-5-phenyl-8-hydroxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	331
133	2,4-diamino-5-(3-fluoro-phenyl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	363
134	2,4-diamino-7-bromo-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	347, 349
135	2,4-diamino-5-phenyl-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile	345

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[000201] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

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**[000202]** In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

**[000203]** As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is  
5 intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.